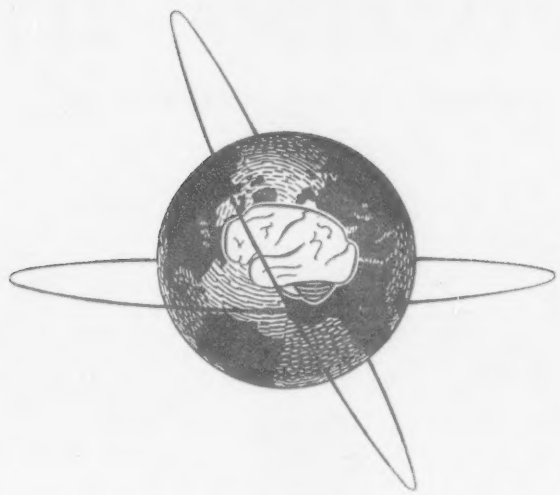
# ELECTROENCEPHALOGRAPHY
## AND
# CLINICAL NEUROPHYSIOLOGY

AN INTERNATIONAL JOURNAL



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# ELECTROENCEPHALOGRAPHY
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## L'EXPLORATION PHARMACODYNAMIQUE CORTICO-SOUS-CORTICALE ET SES CRITÈRES ÉLECTROGRAPHIQUES. LA DÉTERMINATION D'UN FOYER LÉSIONNEL CHEZ L'HOMME PAR LA TECHNIQUE PENTOTHALIQUE


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Les travaux neurophysiologiques de ces dernières années ont mis l'accent sur le rôle que jouent les structures sous-corticales dans le déterminisme et contrôle de l'électrogénèse cérébrale spontanée ou modifiée par voie pharmacologique. Les variations que subit l'EEG d'un sujet normal au fur et à mesure d'une narcose progressive, donnent forme à de véritables stades électrographiques dont chacun correspond à une symptomatologie clinique donnée et à des mécanismes neurophysiologiques précis; parmi ceux que nous connaissons, les phénomènes d'activation — inhibition des centres sous-corticaux réglant l'électrogénèse corticale, tiennent une place essentielle. Une lésion de ces centres modifie de façon spécifique l'un, l'autre ou même l'ensemble de ces stades électrographiques, — à un moment où l'EEG spontané peut se révéler parfaitement normal. Le but de ce travail est de démontrer les possibilités qu'offre un agent pharmacodynamique tel le Pentothal pour localiser un processus intra-crânien et en particulier un processus lésant ou comprimant les structures régulatrices ou les voies qu'empruntent leurs incitations pour atteindre le cortex cérébral.

### MATÉRIEL

Les résultats de ce travail se basent sur l'examen EEG de 360 malades choisis dans le matériel d'un service mixte de Neuro-chirurgie et de Neurologie; sur chaque malade a été posé un diagnostic précis. Dans les conclusions et élaborations de cette étude ont surtout été utilisées les données fournies par les cas neuro-chirurgicaux auxquels l'intervention, l'autopsie ou les techniques neuro-chirurgicales habituelles (artériographies carotidienne ou vertébrale, pneumo-encéphalographies fractionnées ou ventriculographies) apportaient une focalisation particulièrement précise. Parmi ces cas, de nombreuses tumeurs: ici encore, nous avons cru bon d'insister sur les résultats fournis par les tumeurs bien délimitées — en accordant délibérément moins d'importance aux enregistrements des tumeurs largement infiltrantes dont une délimitation nette s'avère souvent impossible. Dans le lot de ces tumeurs, nous nous sommes surtout intéressés aux cas sans ou avec peu d'hypertension intra-crânienne, présentant de ce fait en particulier en ce qui concerne les tumeurs du tronc à leur début, des tracés spontanés souvent normaux ou non-spécifiques.

Nombreux ont été les malades qui ont bénéficié de plusieurs examens pentothaliques — avant et après intervention. Il est inutile de dire finalement que tous nos malades ont subi avant la ou les stimulations pentothaliques un ou plusieurs enregistrements suivant les techniques classiques (EEG spontané, sous hyperpnée, parfois avec stimulations cardiazolique ou lumineuse intermittente).

Le matériel examiné comporte: des tumeurs du tronc cérébral inférieur (2), du tronc cérébral supérieur (3), des tumeurs cérébelleuses (9), des tumeurs hypophysaires (9), une tumeur thalamique et 1 tumeur du 3ième ventricule, des gliomes infiltrant (8) ou non les noyaux centraux (27), des néoformations localisées corticales ou immédiatement sous-corticales (astrocytomes, hématomes intra-parenchymateux, métastases) (21), des méningiomes de l'étage moyen ou antérieur (9), des méningiomes parasagittaux antérieurs et postérieurs (7), des processus inflammatoires (9) ou traumatiques (4) de la région mésencéphalo-diencéphalique, des affections vasculaires ou circulatoires délimitées (22), et enfin des affections cérébrales diverses offrant de par leur nature, leur point de départ ou par les troubles qu'elles entraînent, un intérêt pour l'électroencéphalographiste (affections dégénératives diencéphalohypophysaires (11), chorées (3), maladies de Parkinson (11), crises hypersomniques (6), épilepsies focalisées et généralisées (61), hystéries en périodes de crises (2), névropathies constitutionnelles graves (27), troubles post-commotionnels intenses (6), maladies mentales telles la schizophrénie catatonique (4), etc.). Les conclusions qui découlent de la lecture des EEG sous Pentothal ne peuvent faire ici que l'objet d'un exposé sommaire et quelque peu rigide; nous espérons lors de publications ultérieures montrer les données fines et plus subtiles auxquelles nous a habitué l'étude de ces tracés. Ces données ont souvent été d'une aide précieuse pour mieux localiser un foyer ou mettre en évidence les structures sous-corticales impliquées dans le processus lésionnel (Schneider et Thomalske 1954); bien plus, les relations qui nous ont paru exister entre la morphologie de certains grapho-éléments et certains symptômes cliniques présentés par le malade font entrevoir les possibilités qu'offre la stimulation pentothalique à la pratique EEG courante — en particulier au diagnostic de toute une série de troubles fonctionnels connus pour n'exercer aucune modification sur le tracé EEG spontané.

## TECHNIQUE

Tout procédé d'activation exige une technique rigoureuse et toujours identique. Les examens ont été pratiqués avec des appareils à 8 ou 15 plumes (E.C.E.M.) dont les caractéristiques (filtres de fréquence et constantes de temps) doivent être rigoureusement identiques pour chaque canal.

Les produits utilisés ont été le Pentothal Abbott ou son homologue français le Nesdonal en solution à 5%. Le Pentothal nous a souvent paru avoir une action plus rapidement dépressive que le Nesdonal. Ces drogues sont injectées en dent de scie à raison de 1 cc. toutes les 30 sec. Avant de subir l'examen sous Pentothal et afin d'éviter le spasme éventuel de la glotte, le sujet reçoit une prémédication à l'atropine (¼ mgr. i.v.) — dose qui n'exerce, comme nous avons pu le constater, aucun effet sur l'EEG. Avec cette technique (injections lentes, prémédication atropinique et position allongée du malade) nous n'avons jamais observé d'accident (spasme de la glotte ou arrêt respiratoire de longue durée); par ailleurs nous n'avons jamais eu la main forcée à l'intubation ou à la respiration artificielle — ceci même dans des cas de tumeurs du tronc cérébral qui montraient déjà spontanément quelques troubles respiratoires ou de déglutition. Si certains malades ont présenté un léger arrêt respiratoire en début de narcose, celui-ci n'a jamais dépassé 5-15 sec. au bout desquelles la respiration revenait spontanément. Nous conseillons cependant, au cours d'anesthésies profondes (au-delà de 1 gr. de Pentothal) de "luxer" la mâchoire inférieure vers l'avant et le haut de façon à éviter un blocage mécanique éventuel des voies respiratoires par chute de la langue. Il nous a enfin semblé bon de donner à certains malades particulièrement sensibles au Pentothal — et qui au cours de l'examen présentaient un peu de cyanose des lèvres — de l'oxygène en circuit demi-ouvert et par l'intermédiaire d'un masque bien adaptable.

### *Considérations préliminaires.*

Avant de mettre en pratique cette nouvelle technique d'activation chez le sujet malade, nous avons procédé à des examens répétés d'individus normaux dont le nombre s'élève aujourd'hui à 56. Le Pentothal injecté suivant la technique sus-décrite, donne naissance à 4 stades électrographiques dont chacun se caractérise par des grapho-éléments définis par leur mode d'apparition, leur localisation, leur morphologie et durée ainsi que par les doses de Pentothal nécessaires pour les déclencher [1] (fig. 1) (Schneider et col. 1951; Schneider 1954 a et b).

1. Le stade d'induction anesthésique (fig. 1 B) (1-5 mg/kg.) se caractérise par des activités rapides de 25-30 c/sec. débutant en bouffées de courte durée (½ à 1 sec.) sur les dérivations pré-frontales et pré-centrales pour

[1] Ces doses sont individuelles et pour un sujet normal donné, souvent variables suivant son état d'excitabilité.

s'étendre progressivement sur les régions temporales et post-centrales des deux hémisphères; de telles activités ne sont modifiées ni par l'ouverture-fermeture des yeux, ni par la stimulation lumineuse intermittente.

Ce stade que nous avons également intitulé stade d'activation se manifeste du point de vue électrographique par une hyperactivité psychomotrice plus ou moins importante ainsi que par des phénomènes d'hyperexcitabilité neuronique sur les mécanismes et effets desquels nous reviendrons ultérieurement.

2. Le stade de début de sommeil (4-8 mg/kg.) (fig. 1 C): s'exprime électrographiquement par les ''spindle bursts'' caractéristiques; leurs éléments prédominent en voltage et régularité sur les régions antérieures des 2 hémisphères; ils ont une fréquence initiale de 16-20 c/sec. qui va peu à peu en diminuant jusqu'à 5-6 c/sec. Essentiellement contrôlé par le ''pace-maker'' thalamique de Dempsey-Morison, ce stade ne devient manifeste qu'après blocage du système réticulé d'éveil.

3. Le stade de sommeil proprement dit (8-15 mg/kg.) (fig. 1 D) s'objective à l'EEG par des ondes lentes, amples polymorphes de 2-5 c/sec. entrecoupées d'activités plus rapides, diffuses sur l'ensemble des deux hémisphères.

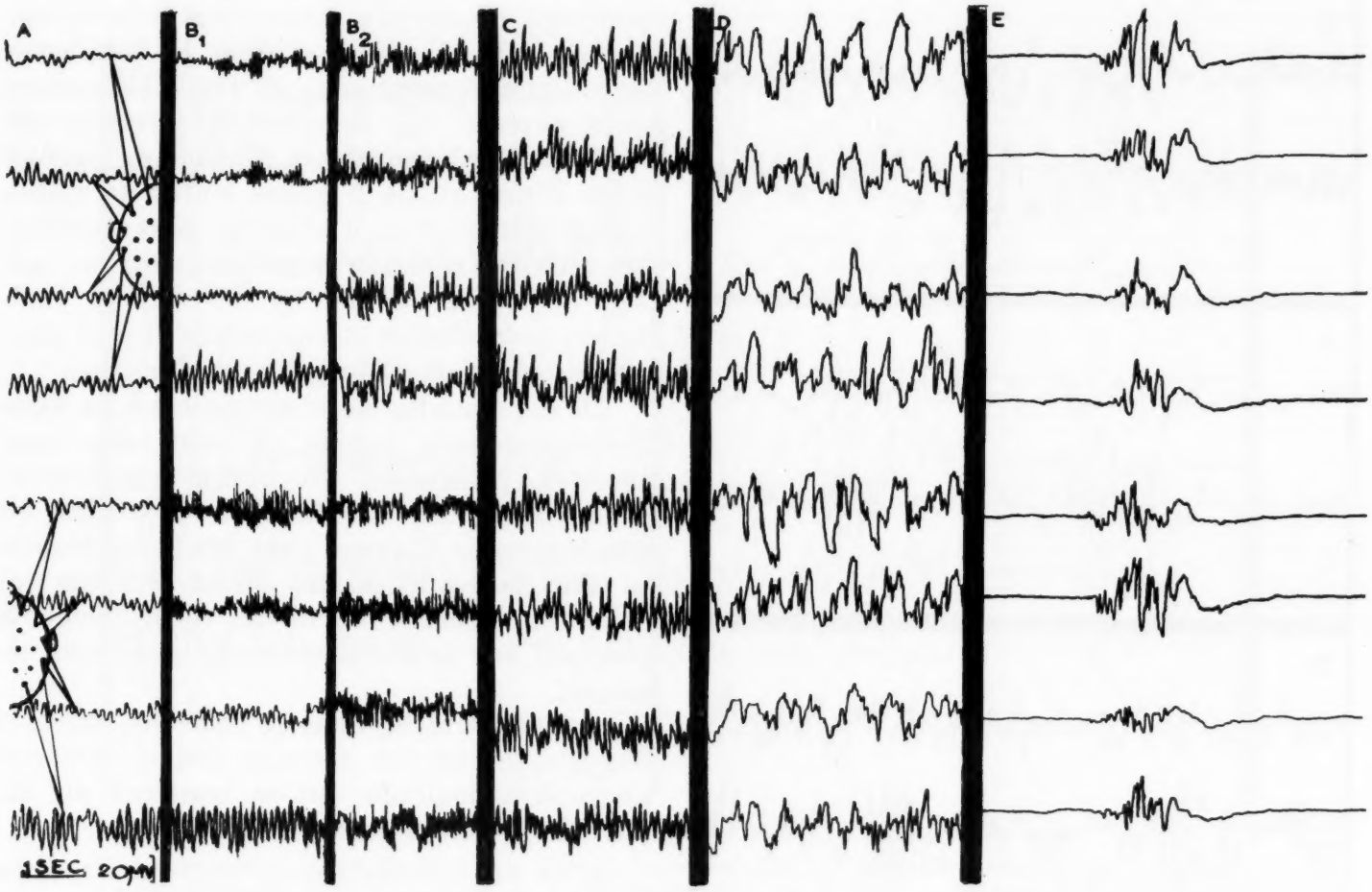


Fig. 1

Les 4 stades pentothaliques du sujet normal:
A) tracé avant injection;
$B_1$ et $B_2$) stade électrographique rapide (1-5 mg/kg.);
C) stade des ''spindle bursts'' (4-8 mg/kg.);
D) stade des ondes lentes polymorphes (8-15 mg/kg.);
E) stade des silences électriques et des complexes-K (à partir de 15-20 mg/kg.).

4. Le stade de sommeil profond et anesthésique (au-delà de 15-20 mg/kg.) (fig. 1 E) se manifeste à l'EEG par des silences électriques de plus en plus étendus, entrecoupés de paroxysmes électriques dénommés complexes-K. Chez le sujet normal, ces complexes-K induits par Pentothal surviennent de façon

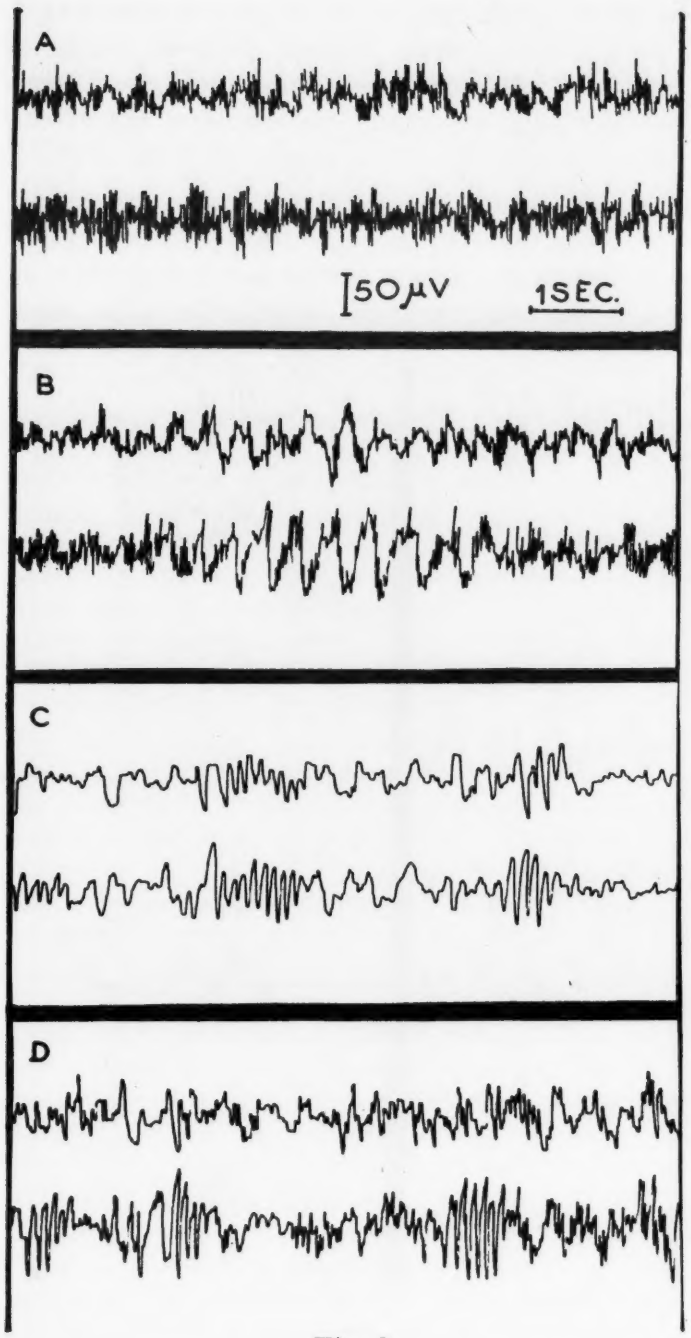


Fig. 2

Transsections étagées du tronc cérébral chez le chat au cours du stade d'induction anesthésique. Cortex sensori-moteur-cortex acoustique (les résultats sont valables aussi bien pour l'induction au Pentothal que pour l'induction à l'éther) ;

A) tracé pris immédiatement après transsection bulbaire: conservation du stade électrographique rapide;

B) tracé après transsection pontine en regard du noyau principal du trijumeau: conservation du stade électrographique rapide entrecoupé parfois de paroxysmes lents à 2-3 c/sec. surchargés d'activités rapides;

C) tracé après transsection mésencéphalique immédiatement en arrière des tubercules quadrijumeaux: disparition brutale des activités rapides et apparition des ondes lentes rythmiques caractéristiques de la déafférentation;

D) tracé pris une heure après transsection mésencéphalique (bonnes préparations avec chute tensionnelle corrigée). Ces animaux, soumis à une nouvelle induction anesthésique, continuent à présenter un tracé de déafférentation dont les éléments cependant sont surchargés d'activités rapides toutefois pauvres et d'apparition sporadique.

→

simultanée et bilatérale synchrone sur l'ensemble des deux hémisphères. Ils se présentent sur les dérivations préfrontales et précentrales supérieures sous la forme d'une onde ample de 2-3 c/sec., diphasique positive-négative pratiquement inexistante sur les dérivations plus postérieures. Chez le sujet normal, cette onde est suivie de quelques ondes à 4-5 c/sec. de plus faible voltage et diffuses sur l'ensemble des deux hémisphères — le tout surchargé d'activités rythmiques répétitives rapides à 14-15 c/sec. et dont la fréquence diminue progressivement au fur et à mesure de la narcose. Le complexe-K terminal est constitué par l'onde lente diphasique parfois suivie d'une ou de 2 ondes lentes de faible voltage dépourvues d'activités plus rapides. Les activités répétitives prédominent en voltage et régularité sur les dérivations antérieures précentrales et temporales et sont pauvres sur les dérivations plus postérieures [1].

De ces 4 stades electrographiques, le stade électrographique rapide et celui des complexes-K présentent un intérêt particulier. Sous l'influence d'affections corticales ou sous-corticales diverses, ces stades subissent en effet des modifications caractéristiques qui nous ont toujours fourni des renseignements précieux sur la localisation du processus lésionnel.

Avant d'entrer dans le cœur du sujet, il importe de décrire certains des mécanismes neurophysiologiques qui se trouvent au départ de ces 2 stades électrographiques.

A. Le stade électrographique rapide se caractérise du point de vue clinique par une hyperactivité psychomotrice passagère d'une durée variable suivant le mode d'administration du narcotique et l'état constitutionnel du sujet (Schneider et col. 1952; Schneider 1954 a et b). Il peut dans certains cas s'objectiver par une agitation motrice plus ou moins importante avec mouvements excessifs et incoordonnés, dé-

[1] L'injection de Pentothal chez le chat provoque 4 stades électrographiques dont les éléments sont très comparables sinon identiques à ceux décrits chez l'homme (Schneider et col. 1952).

charges logorrhiques, troubles associatifs et fuite des idées, euphorie, hypersensibilité à la douleur, augmentation de la fréquence respiratoire du pouls et de la tension artérielle avec une conscience et une motilité volontaire parfaitement bien conservées.

Du Pentothal goutte à goutte et à faibles concentrations déclenche un stade électrographique rapide qui peut s'étendre parfois sur 1-2 heures et s'accompagner *a*) chez le chat, de spikes en volées continuelles avec leurs corollaires myocloniques; *b*) chez l'épileptique temporal, d'une recrudescence des anomalies épileptogènes pouvant dans certains cas aller jusqu'à la crise (Schneider et col. 1952; Schneider et Thomalske 1955; Schneider 1954 b, 1955).

Ce stade s'accompagne donc d'un abaissement net du seuil d'excitabilité neuronique signalé par Swank et Watson 1949, Schutz et Caspers 1953, Rosenkoetter 1953 et nous-mêmes (Schneider et col. 1952; Schneider 1954 b); il a un caractère électrographique essentiellement cortical (Brazier 1954) et ses activités rapides ne s'observent sur aucune des structures diencéphaliques qu'Okuma et col. (1954) et nous-mêmes (Schneider et col. 1952) ont eues l'occasion d'enregistrer; il semble par contre largement conditionné par les incitations d'une réticulée mésencéphalique en hyperactivité passagère (Arduini 1954; Schneider et col. 1951; Schneider et Thomalske 1955; Schneider 1954 b, 1955).

Les transsections étagées du tronc cérébral montrent le rôle que jouent les structures mésencéphaliques dans le déclenchement et maintien de ce stade électrographique (fig. 2) (Schneider et col. 1951; Schneider 1954 b, 1955; Schneider et Thomalske 1955; Rossi et Zirondoli 1954 et 1955).

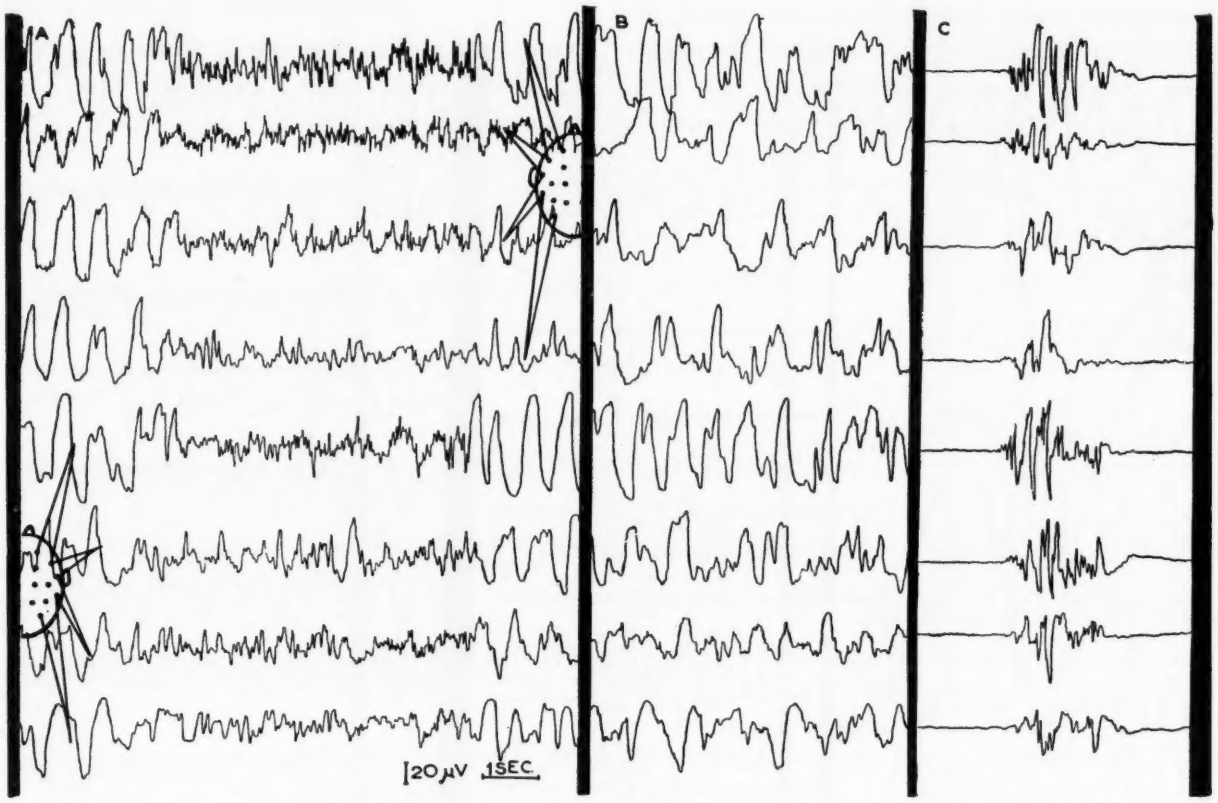


Fig. 3

Tracés pris chez une malade opérée 3 mois auparavant d'une strumite grave et qui a présenté progressivement le tableau clinique d'une encéphalite de la région mésencéphalo-diencéphalique vérifiée à l'autopsie:
A) tracé spontané pratiqué les premiers jours de sa maladie avant l'apparition des ondes lentes caractéristiques des lésions de cette région. Ce tracé se caractérise par des activités rapides de 15-25 c/sec. prédominant sur les dérivations antérieures et entrecoupées de paroxysmes électrographiques lents monomorphes. (Tracés sous Pentothal: B + C.)
B) dès les 1ers cc. de Pentothal on tombe d'emblée dans le stade des ondes lentes monomorphes de 2-5 c/sec.;
C) stade des silences électriques et des complexes-K.

Certains sujets — abstraction faite des barbiturisés chroniques — présentent déjà à l'EEG spontané des activités rapides comparables à celles du stade d'activation pentothalique. Ces activités vont habituellement de pair avec des troubles du comportement qui ont fait l'objet d'une publication antérieure (Schneider 1955): hyperactivité psychomotrice, tics, mouvements stéréotypés souvent scéniques, labilité af-

fective, troubles associatifs, fuite des idées chez des sujets dont certains ont présenté fortuitement et à intervalles lointains une ou deux crises convulsives généralisées [1]. De tels tracés ont également été signalés par Gastaut (1954), Jasper (1953), Loeb (1953) dans certaines lésions de la région mésencéphalo-diencéphalique. Nous-mêmes avons à notre disposition plusieurs de ces exemples (in Gastaut 1953; et fig. 3).

B. Au complexe-K de l'homme correspond la "décharge secondaire" de l'animal. L'onde lente diphasique faisant le début du complexe constitue la réponse d'un système de projection diffuse mise en branle par une incitation périphérique ou endogène. Les activités répététives qui lui font suite — et qui font défaut à la décharge secondaire — paraissent avoir une origine plus locale, vraisemblablement thalamo-corticale ou corticale et semblent déclenchées par l'afférence non-spécifique à son arrivée sur le cortex cérébral. A l'encontre du stade électrographique rapide qui est bloqué par transsection mésencéphalique, la décharge secondaire spontanée n'est nullement inhibée par une telle section. Il semble que cette réponse — comme d'ailleurs le complexe-K de l'homme — puisse avoir un départ aussi bien mésencéphalique (Dempsey-Morison 1941) que supra-mésencéphalique.

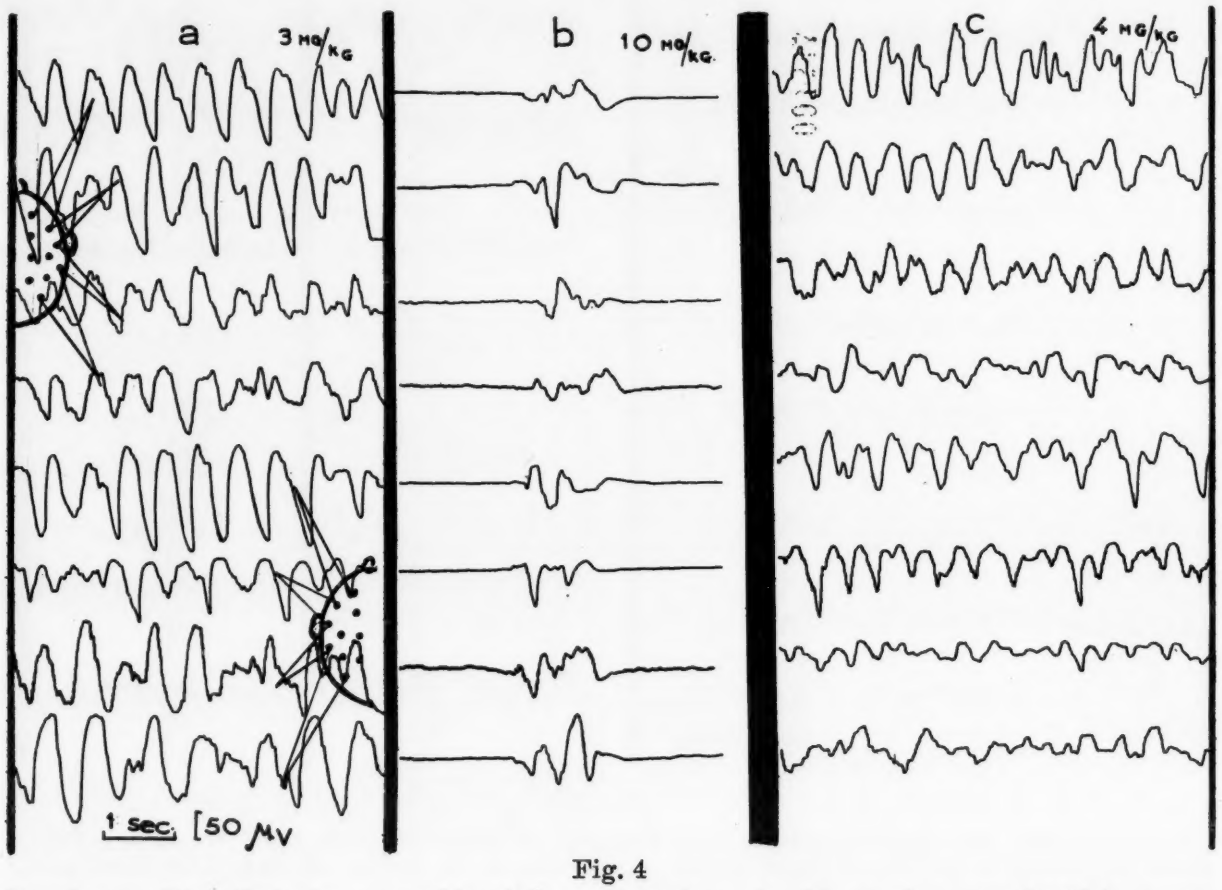


Fig. 4

Tracé sous Pentothal chez un schizophrène catatonique (a, b) et chez une hystérie grave en période aiguë (c).
A noter 1° l'absence complète du stade électrographique rapide (a et c) et 2° la morphologie particulière du complexe-K (b).

Ici encore toute une série d'affections du tronc cérébral supérieur, traumatismes crâniens, tumeurs mésencéphaliques, encéphalites etc.... peuvent donner lieu à l'EEG spontané à un tableau électrographique voisin de celui observé au cours du stade des silences électriques ou des complexes-K pentothaliques et dont les éléments semblent correspondre à une réaction d'éveil larvée, strictement électrique.

La diversité des affections qui font l'objet de ce travail rend difficile une description purement analytique des nombreuses perturbations que peuvent manifester les stades pen-

[1] En regard de ces sujets qui présentent à l'EEG spontané ces activités électrographiques rapides et une hyperexcitabilité et instabilité psychomotrice, nous désirons opposer les résultats fournis par les stimulations pentothaliques dans 4 cas de stupeur catatonique et 2 cas d'hystérie grave avec "crises en arc de cercle". Tous ces malades ont montré une absence complète du stade d'activation pentothalique — le sujet tombant d'emblée dès les premiers cc. dans un stade d'ondes lentes monomorphes dépourvues d'activités rapides (fig. 4).

tothaliques. Au risque de simplifier de façon excessive les données multiples que nous apportent ces stimulations chez le sujet malade, nous avons délibérément accordé à ce travail un plan plus compréhensible, en grande partie dicté par des considérations d'ordre anatomo-physiologique et pratique.

*Résultats chez le sujet malade.*

1. *Affections du tronc cérébral inférieur et affections du cervelet ne donnant pas lieu à une compression du mésencéphale.*

Quatre cas dont 1 épendymome du plancher du IV ventricule, 1 tumeur du toit du IV ventricule et 2 astrocytomes des hémisphères cérébelleux postérieurs. Ces malades ont été pris au début de l'affection et ont présenté de ce fait un syndrôme d'hypertension intra-crânienne peu accentué et un EEG spontané normal ou légèrement dysrythmique.

Tous ces cas ne modifient en aucune façon les 4 stades électrographiques normalement induits par Pentothal — autant en ce qui concerne la morphologie de leurs graphoéléments que la durée respective de chaque stade et les doses de narcotique nécessaires pour les induire. Le complexe-K survient toujours de façon bilatérale synchrone sur l'ensemble des deux hémisphères. En présence d'un malade ayant une symptomatologie de la fosse postérieure et des stades pentothaliques normaux, nous ne nous sommes jamais trompés en affirmant un processus lésionnel bulbaire ou cérébelleux sans compression du mésencéphale — à l'exception toutefois des cas qui présentent déjà d'emblée un important syndrome clinique et électrographique d'hypertension intra-crânienne.

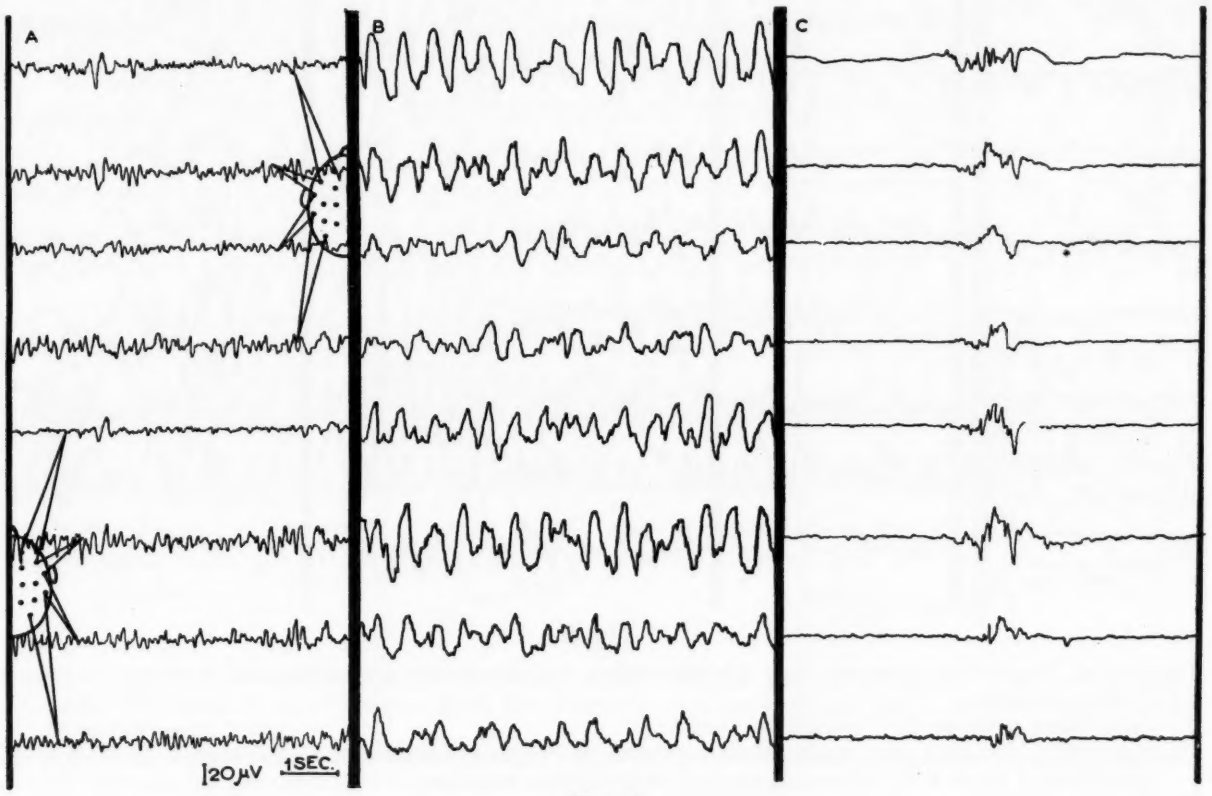


Fig. 5

Tracé sous Pentothal dans un cas d'obstruction tumorale de l'aqueduc de Sylvius (médulloblastome) :
A) tracé spontané;
B) absence du stade électrographique rapide — le tracé se caractérise dès les 1ers cc. de Pentothal (3 mg/kg.) par des ondes lentes monomorphes de 2-4 c/sec.;
C) stade des silences électriques et complexes-K qui surviennent avec des concentrations anormalement faibles de Pentothal (10 mg/kg.). A noter le synchronisme interhémisphérique des complexes-K.

2. *Affections du tronc cérébral supérieur ou encore affections de la fosse postérieure ou du cervelet déterminant secondairement une compression du mésencéphale.*

Dix-sept cas dont 10 néoformations (1 méningiome de la fosse postérieure, 1 médul-

loblastome mésencéphalique, 1 obstruction de l'acqueduc de Sylvius par kyste, 6 tumeurs du vermis ou des hémisphères cérébelleux antérieurs, 1 ramollissement kystique du cervelet) et 7 cas de névraxite du tronc avec hypertension intra-crânienne, stase papillaire et symptomatologie mésencéphalique.

Même dans les cas où l'EEG spontané se montre normal, l'EEG sous Pentothal donne lieu à des perturbations qui peuvent prendre 4 aspects différents; ces perturbations s'exercent uniquement sur le stade électrographique rapide et s'expriment soit par:

*a*) une absence complète du stade d'activation — à la place de ses activités rapides surviennent ou des ''spindle bursts'' lents a 5-6 c/sec. ou des ondes amples plus ou moins monomorphes d'une fréquence de 2-4 c/sec. diffuses sur l'ensemble des deux hémisphères (fig. 5);

*b*) une réduction importante de la durée de ce stade électrographique rapide;

*c*) une inversion des stades 1 et 2 avec apparition initiale de ''spindles'' lents et vers la fin du stade d'activation (fig. 6);

*d*) l'apparition de paroxysmes électrographiques se manifestant sous la forme d'ondes lentes amples monomorphes de 2-4 c/sec. pauvres en éléments rapides et bloquant de façon intermittente les activités de 20-30 c/sec. normalement induites par le narcotique (fig. 6).[1] Tous ces cas se caractérisent enfin par une diminution nette des doses de Pentothal nécessaires pour induire

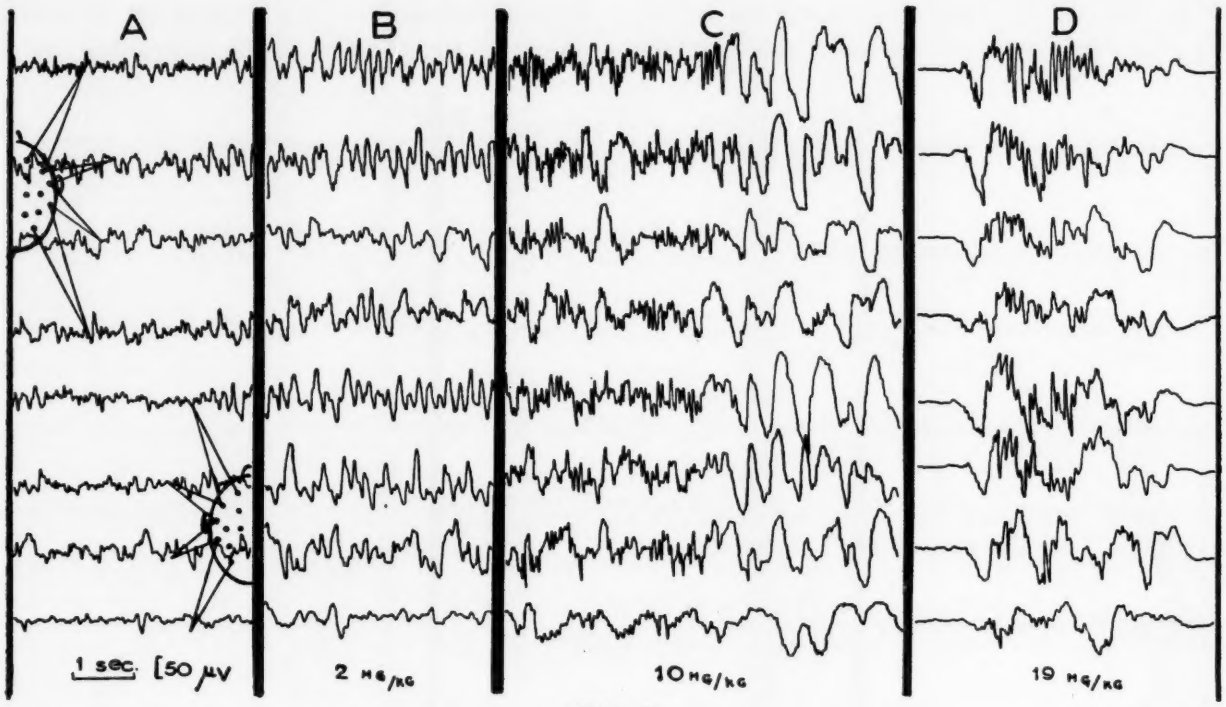


Fig. 6

Tracé sous Pentothal dans un cas d'obstruction par kyste de l'aqueduc de Sylvius:
A) tracé spontané;
B) apparition précoce de ''spindles'' lents;
C) apparition tardive du stade électrographique rapide, entrecoupé de temps à autre de paroxysmes lents à 1-3 c/sec. dépourvus d'activités rapides;
D) stade anesthésique profond avec complexes-K normaux et synchrones.

les divers stades électrographiques — comme l'ont également noté Mallin et ses col. (1954).

Dans tous ces cas de lésions ou de com-

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[1] Certaines affections mésencéphalo-diencéphaliques peuvent d'ailleurs présenter à l'EEG spontané des activités rapides identiques et les mêmes ''paroxysmes'' que nous venons de décrire sous Pentothal (fig. 3).

Deux cas d'obstruction de l'aqueduc qui avant intervention et sous Pentothal avaient donné lieu à ces paroxysmes électrographiques ont montré après élimination de l'obstacle un tracé pentothalique absolument normal.

Il convient cependant de s'assurer pour chaque cas que ces paroxysmes lents ne sont pas provoqués par un arrêt respiratoire de plus ou moins longue durée.

pressions limitées à la région mésencéphalique, les complexes-K restent inchangés, survenant toujours de façon bilatérale synchrone sur l'ensemble des deux hémisphères (fig. 6).

Nous tenons à signaler — et cette digression permettra d'entrevoir les possibilités qu'offre la stimulation pentothalique à la pratique électrographique courante — que certaines affections dites fonctionnelles peuvent donner lieu sous Pentothal à des perturbations identiques à celles que nous venons de décrire pour les lésions ou compressions mésencéphaliques. De telles perturbations plaident manifestement en faveur du rôle que pourraient jouer les mécanismes mésencéphaliques dans le déterminisme de la symptomatologie de ces affections (Schneider et Thomalske 1954):

*a*) de nombreux cas d'épilepsie dite essentielle dont les tracés EEG spontanés et sous hyperpnée se montrent normaux (fig. 7). Ces données nous ont souvent permis d'affirmer la participation de mécanismes sous-corticaux à l'activité d'un foyer épileptogène supposé cortical;

*b*) certaines névropathies graves avec déséquilibre neuro-végétatif accentué ainsi qu'un certain nombre de post-commotionnés crâniens aux séquelles subjectives importantes.

Ces résultats ont leur importance et sont là pour démontrer que chaque stimulation pentothalique constitue un cas d'espèce dont il convient de considérer les données électrographiques en regard des caractères constitutionnels du sujet.

3. *Affections des structures diencéphaliques basales à cheval sur la ligne médiane.*

Nous avons compris dans ce groupe les tumeurs hypophysaires pures ou comportant des kystes supra- et rétro-sellaires plus ou moins importants (9 cas) (fig. 8). Tous ces cas montrent des perturbations plus ou moins marquées du stade d'activation; ces perturbations sont cependant de moindre importance et se manifestent uniquement par les paroxysmes électrographiques sus-décrits. Dans les affections basales médianes, les complexes-K sont normaux, survenant de façon bilatérale synchrone sur l'ensemble des deux hémisphères. Nous avons par ailleurs enregistré toute une série d'affections diencéphalo-hypophysaires (11 cas) avec EEG spontané normal et qui sous Pentothal ont donné naissance à ces mêmes paroxysmes lents.

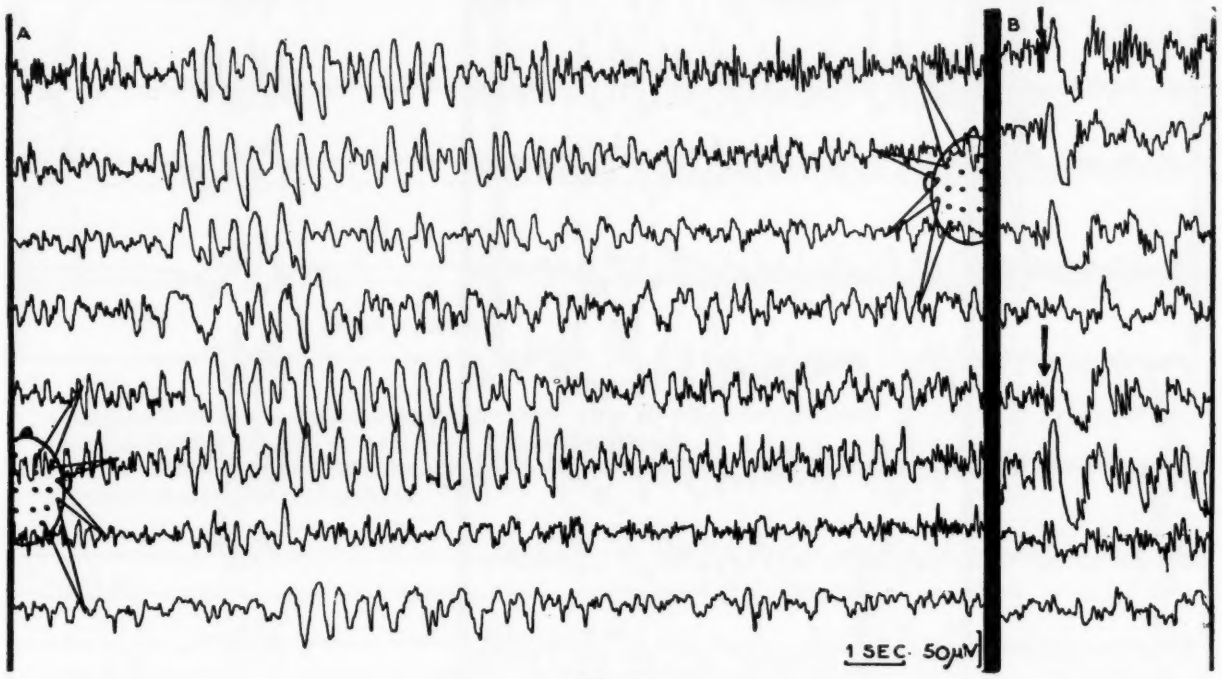


Fig. 7

Résultats de la ''stimulation pentothalique'' dans certains cas d'épilepsies dites essentielles:
A) stade d'induction anesthésique dont les éléments rapides sont de temps à autre entrecoupés de paroxysmes lents;
B) apparition de paroxysmes prenant la forme de pointes-ondes bilatéraux synchrones sur les dérivations précentrales et antérieures des deux hémisphères.

4. *Affections des portions latérales du diencéphale basal.*

Dans ce groupe il convient de distinguer:

*a*) les lésions du diencéphale basal postérieur. D'origine traumatique (4 cas) ou

toxico-infectieuse (9 cas), ces cas se caractérisent en général par des altérations plus ou moins marquées de l'EEG spontané et montrent sous Pentothal i) le plus souvent une absence complète du stade d'activation (11 cas), plus rarement des paroxysmes lents importants (2 cas), ii) en ce qui concerne le stade des complexes-K, un phénomène nouveau sous la forme de décalages discrets et intermittents de ces complexes électrographiques qui se manifestent sur l'un ou l'autre des 2 hémisphères avec un léger retard de ½ à 1 sec. (fig. 9 b) ;

Dans ces cas le stade électrographique rapide est le plus souvent absent ou fruste et alors entrecoupé de paroxysmes lents — mais ces perturbations sont toujours de moindre importance en regard des anomalies caractéristiques que présente le stade des complexes-K. Ces complexes-électrographiques montrent en effet un a-synchronisme constant et des décalages interhémisphériques pouvant dépasser 4-5 sec. (fig. 10).[1]

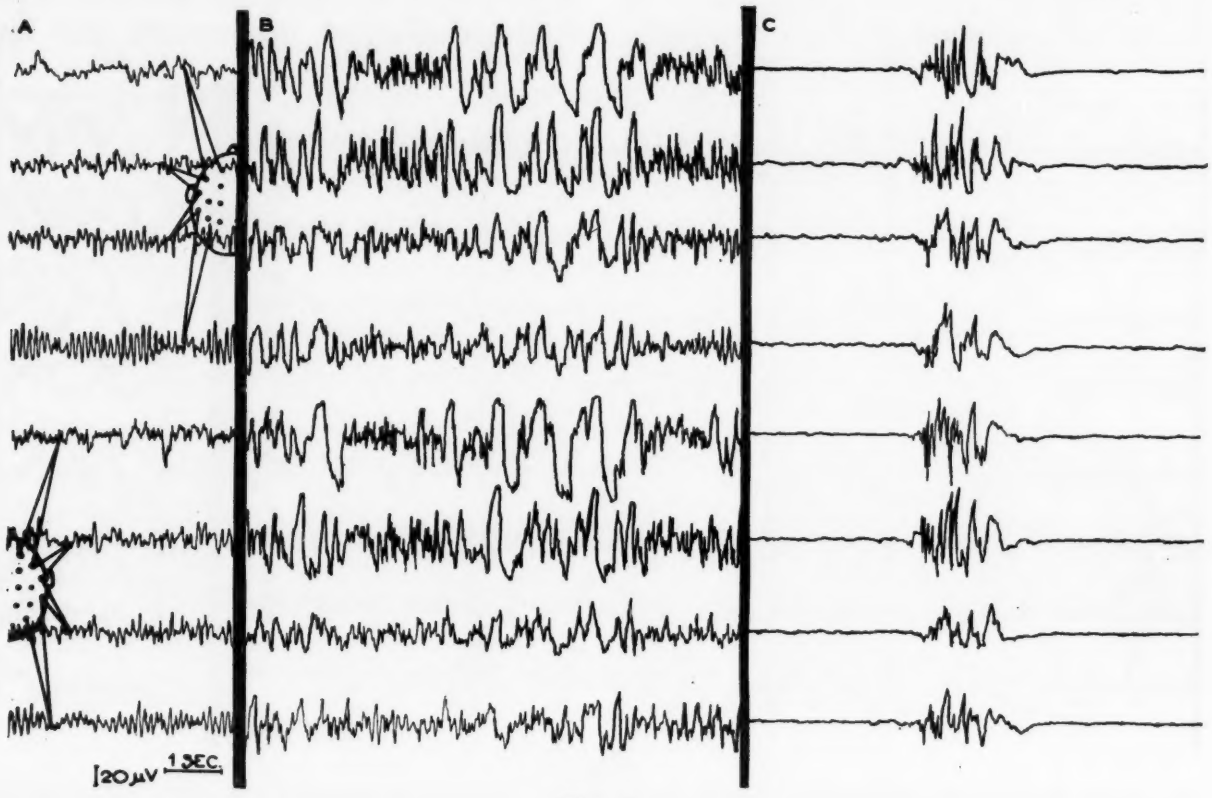


Fig. 8

Tumeur hypophysaire avec kyste supra-sellaire important.
A) tracé spontané;
B et C tracés sous Pentothal:
B) stade électrographique rapide entrecoupé de paroxysmes lents;
C) stade des complexes-K dont il convient de noter le synchronisme.

*b*) les affections qui lèsent les parties latérales du diencéphale basal antérieur. Ces cas comprennent essentiellement des méningiomes de l'étage moyen et parfois antérieur (olfactifs 2, clinoïdien 1, petite aile du sphénoïde 6) comprimant les structures diencéphaliques antérieures par le bas ainsi que des néo-formations frontales profondes (8 cas) qui lèsent ou compriment ces mêmes structures par le haut.

5. *Affections des noyaux gris centraux ou affections des noyaux gris et de la substance blanche avoisinante.*

Les malades de ce groupe seront forcément de nombre restreint; nous avons à notre dis-

[1] Cinq de ces malades atteints de méningiome et enregistrés après intervention, ont montré sous Pentothal une réapparition du stade électrographique rapide et du synchronisme des complexes-K. Un méningiome olfactif sur les 2 enregistrés a montré un stade électrographique rapide normal et des complexes-K synchrones; il s'agissait à l'intervention d'une tumeur très antérieure ne donnant lieu à aucune compression diencéphalique.

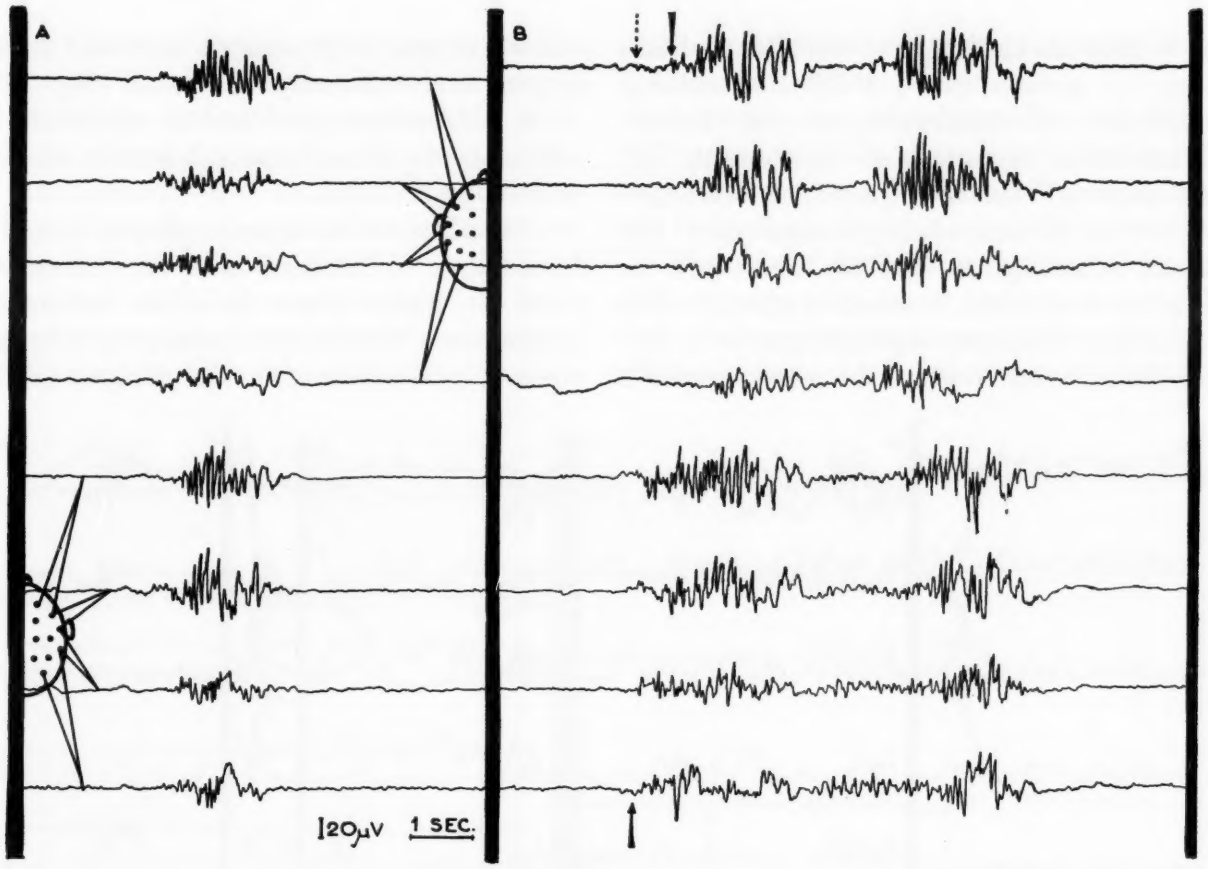


Fig. 9

A) Complexes-K d'une tumeur hypophysaire avec kyste rétro-sellaire. A noter le synchronisme interhémisphérique de ce complexe électrographique;
B) discret décalage interhémisphérique des complexes-K au cours de lésions de la région mésencéphalo-hypothalamique.

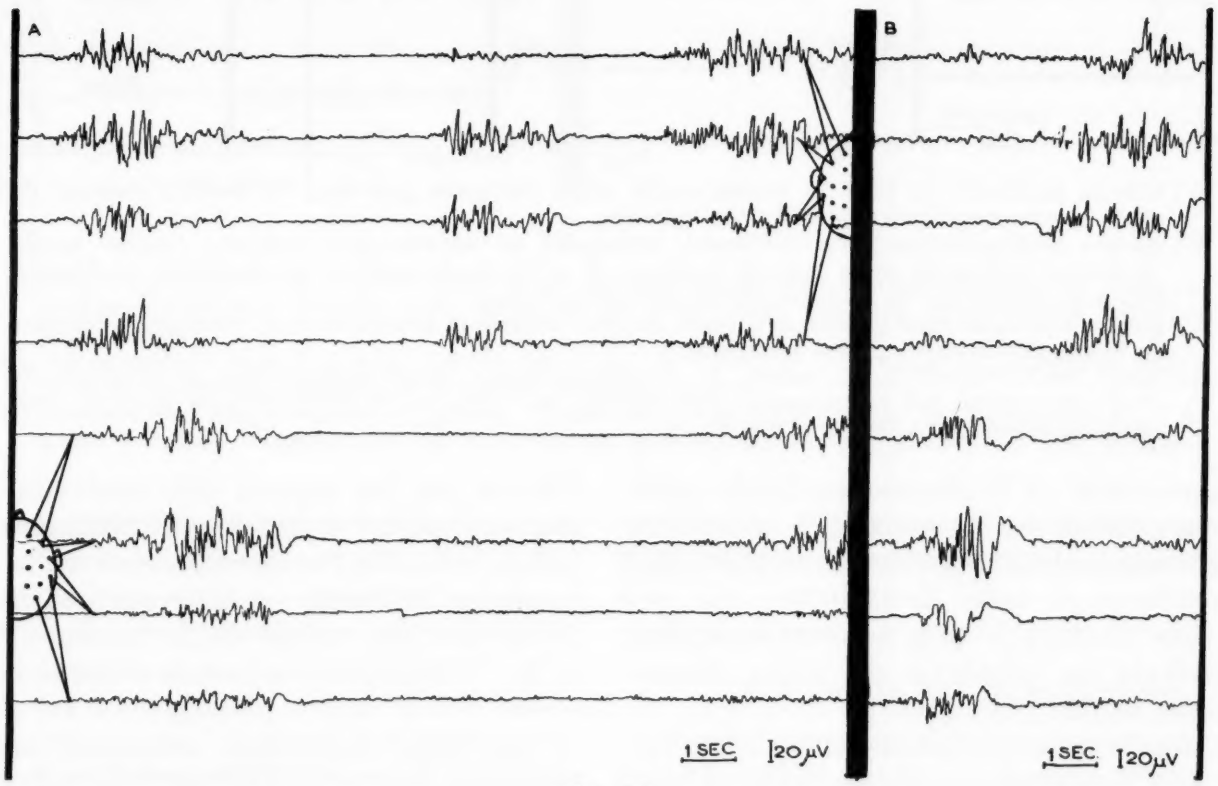


Fig. 10

Stade des complexes-K:
A) dans le cas d'un méningiome de la petite aile du sphénoïde droit;
B) dans le cas d'un gliome frontal para-médian profond gauche.
A noter l'asynchronisme constant de ces paroxysmes électrographiques.

position 1 tumeur thalamique vérifiée à l'intervention — présentant à l'EEG standard des complexes électrographiques en forme de pointes-ondes spontanées survenant en ''waxing-waning'' sur la région fronto-temporale gauche et diffusant légèrement sur les dérivations homologues droites, bien que le malade n'ait à aucun moment présenté des signes cliniques de forme épileptique — 1 tumeur du 3ième ventricule, elle aussi vérifiée

condition que le processus lésionnel ne s'étende pas sur le diencéphale basal (fig. 11 d).

6. *Affections de l'écorce cérébrale ou du cortex et de la substance blanche immédiatement sous-jacente.*

Nous avons ici à notre disposition 19 néoformations délimitées peu envahissantes et plus ou moins superficielles (astrocytomes, métastases, hématomes intraparenchymateux, etc.) et enfin une série de gliomes (21) n'in-

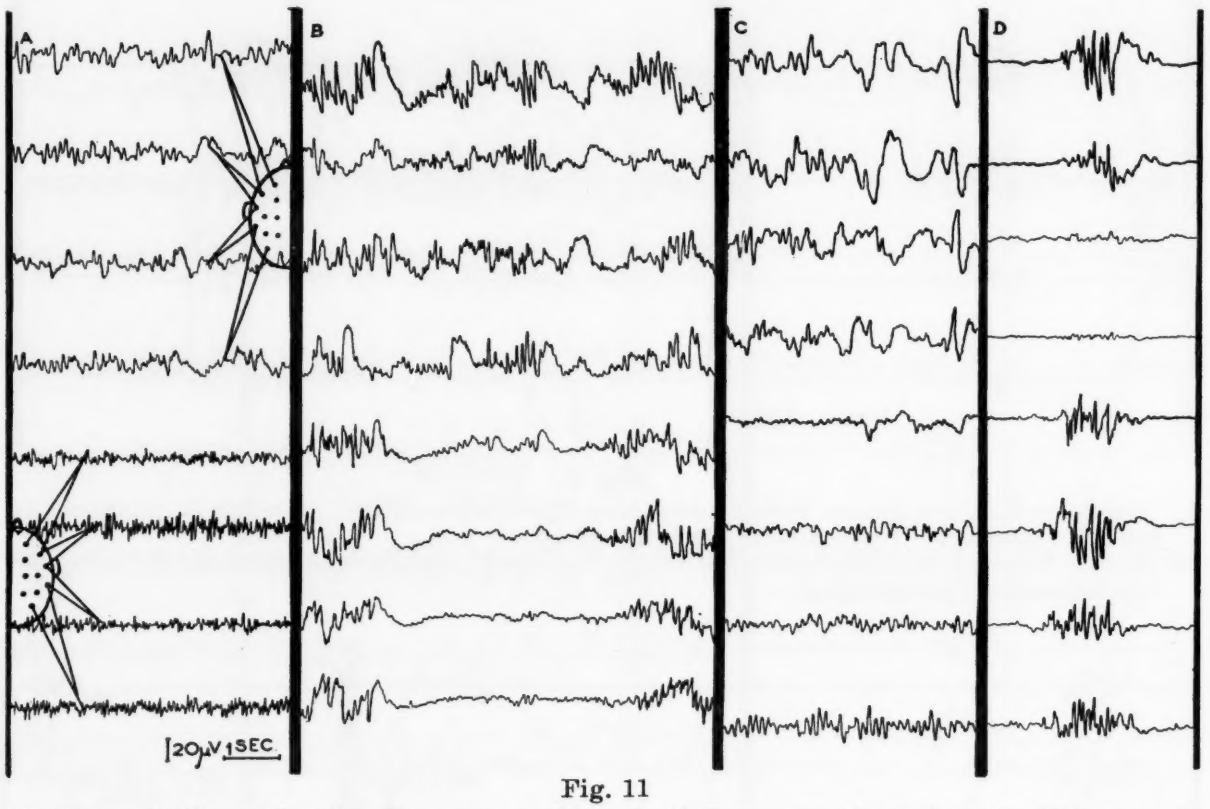


Fig. 11

A) Gliome infiltrant la tête du noyau caudé et le thalamus gauches. A noter l'absence du stade électrographique rapide du côté gauche;
B) gliome hémisphérique droit infiltrant largement les noyaux gris centraux (noyau caudé, thalamus, putamen) et la capsule interne. A noter la dépression intermittente et d'apparition paroxystique de l'électrogénèse cérébrale droite;
C) gliome hémisphérique gauche infiltrant essentiellement le thalamus et la portion postérieure de la capsule interne. Tracé spontané;
D) tracé sous Pentothal. A noter: 1° le synchronisme interhémisphérique du complexe-K, 2° la dépression des composantes postérieures du complexe électrographique gauche, vraisemblablement liée à la lésion capsulaire.

à l'intervention et 8 gliomes profonds infiltrant largement les noyaux gris centraux. Tous ces cas peuvent montrer sous Pentothal soit:

*a*) une absence le plus souvent complète, homolatérale ou bilatérale du stade électrographique rapide (fig. 11 a);

*b*) des dépressions paroxystiques, homolatérales de l'électrogénèse cérébrale (fig. 11 b);

*c*) des complexes-K normaux et dont le synchronisme n'est nullement perturbé — à

filtrant pas les noyaux gris centraux. Dans tous ces cas, les 4 stades pentothaliques manifestent une dépression progressive de l'électrogénèse cérébrale — dépression strictement limitée au lieu même de la tumeur (fig. 12 a, b).[1] Nous n'avons jamais observé de déca-

[1] De telles dépressions deviennent manifestes même dans les cas où l'EEG spontané se montre normal (certains astrocytomes au tracé spontané normal et dont la localisation a été faite par l'EEG sous Pentothal).

lages interhémisphériques des complexes-K; par contre les tumeurs de la région temporo-pariéto-occipitale présentent souvent du côté lésé, des complexes-K dont les éléments postérieurs manifestent un retard d'apparition d'½ à 1 sec. sur les composantes antérieures du même complexe (fig. 12 C).

Il convient enfin de mentionner les données fournies par les méningiomes para-sagittaux antérieurs (4 cas) et postérieurs (2 cas). Le stade électrographique rapide du sujet atteint d'un méningiome para-sagittal antérieur est le plus souvent fruste et souvent entrecoupé de ces paroxysmes électrographiques lents dont nous venons de parler (3 cas); 1 cas sur les 4 enregistrés a montré une abolition unilatérale des activités pentothaliques rapides. De telles perturbations sont vraisemblablement à mettre sur le compte de la compression qu'exerce la tumeur sur le diencéphale antérieur et peut-être sur le cortex limbique antérieur.

Le stade des complexes-K n'est par contre nullement modifié et ses éléments surviennent toujours en bouffées bilatérales synchrones sur l'ensemble des deux hémisphères.

Les modifications qu'exercent les méningiomes para-sagittaux postérieurs sur les divers stades pentothaliques sont plus banales; elles se résument le plus souvent en une dépression de l'électrogénèse cérébrale, localisée à la région temporo-pariétale homolatérale, avec des complexes-K dont le synchronisme est bien conservé.

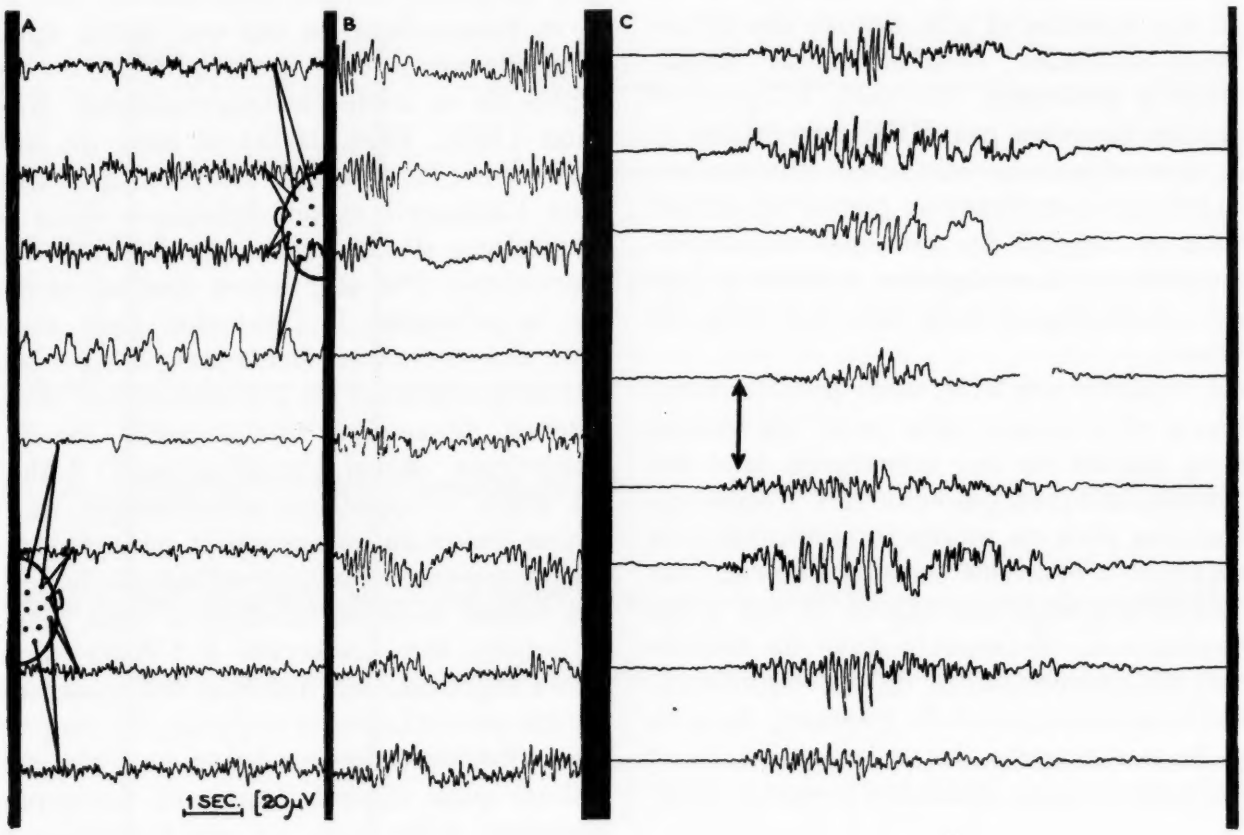


Fig. 12

A) Tracé spontané d'un malade présentant une métastase d'un cancer du sein — tumeur corticale occipitale gauche, bien délimitée et n'infiltrant que peu la substance blanche sous-jacente;
B) même malade sous Pentothal (stade des "spindle bursts"). A noter la dépression marquée de l'activité électrique de la région occipitale gauche;
C) astrocytome temporo-pariétal gauche. Tracé sous Pentothal (stade des complexes-K). A noter le retard d'apparition des composantes postérieures du complexe-K du côté gauche.

## DISCUSSION ET CONCLUSIONS

Parmi tous les agents pharmacodynamiques qu'utilisent les méthodes d'activation pour préciser ou mettre en évidence un foyer électrographique, le Pentothal tient une place

exceptionnelle et ses possibilités sont loin d'être entièrement exploitées.[1]

A l'encontre des variations caractéristiques et toujours identiques que manifeste l'activité électrique cérébrale du sujet sain soumis à une injection de Pentothal, les stades électrographiques normalement induits par ce narcotique subissent des modifications profondes chez le sujet cérébralement malade; le caractère, l'importance de ces perturbations sont étroitement liés à la localisation de la lésion, à son étendue et à la nature des structures sous-corticales éventuellement impliquées dans le processus lésionnel. S'ajoutant aux données fournies par l'EEG spontané et par les investigations cliniques habituelles, cette technique d'exploration permet de situer l'affection en regard des systèmes sous-corticaux contrôlant l'électrogénèse cérébrale (agglomérats neuroniques aussi bien que voies de conduction).

C'est à partir des affections ponto-mésencéphaliques et d'autant plus pour les lésions situées en amont de ces structures, que les stades pentothaliques peuvent être l'objet de perturbations plus ou moins importantes; ces perturbations s'exercent essentiellement sur le stade électrographique rapide et sur celui des complexes-K. Il importe donc de définir les structures responsables de ces manifestations électrographiques et de préciser, dans la mesure de nos moyens, les voies qu'utilisent leurs incitations pour atteindre le cortex cérébral.

Si l'interprétation d'une grande partie des données fournies par la "stimulation pentothalique" s'avère difficile, la constance de certains résultats nous a régulièrement frappé.

En ce qui concerne le stade électrographique rapide:

*a*) les lésions du tronc cérébral inférieur ne provoquent aucune modification de ce stade d'induction anesthésique — à l'exception toutefois des cas comportant une hypertension intra-crânienne importante;

*b*) les lésions du tronc cérébral supérieur ou du tronc cérébral inférieur conduisant secondairement à des phénomènes de compression mésencéphalique déterminent par contre — et même dans les cas ou l'EEG spontané se révèle normal — des modifications importantes de ce stade électrographique. Nos travaux (1951, 1954, 1955) et ceux de Rossi et Zirondoli (1954, 1955) ont montré le rôle que joue l'appareil mésencéphalique dans le déterminisme des activités rapides induites par narcotique. Par son action élective et précoce sur la réticulée, le Pentothal peut mettre à jour des anomalies électrographiques latentes qui ne demandent qu'à s'extérioriser sous l'influence dépressive additionnelle du facteur narcotique. Ainsi s'expliquent, i) l'abolition du stade d'induction anesthésique au cours d'une lésion ou compression importante de la région mésencéphalo-hypothalamique — chez des sujets dont la réaction d'éveil peut parfaitement être conservée à l'EEG spontané, ii) la régression en durée et fréquence des activités pentothaliques rapides, iii) les paroxysmes électrographiques lents caractérisant des lésions plus discrètes ou qui accompagnent certaines affections ne semblant comporter qu'un simple dysfonctionnement de ces structures (certaines formes d'épilepsies dites essentielles, de névropathies graves ou de troubles post-commotionnels importants);

*c*) les affections du diencéphale basal médial ne modifient que pauvrement la morphologie de ce stade électrographique dont les perturbations semblent uniquement s'exprimer par les paroxysmes lents que nous venons de décrire;

*d*) les affections du diencéphale basal latéral déterminent par contre des perturbations considérables de ce stade électrographique — sous la forme d'une abolition ou régression importante de ses éléments — et ces perturbations sont d'autant plus marquées que la lésion est plus postérieure;

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[1] Dans ce travail nous avons volontairement passé sous silence les très nombreuses publications déjà parues sur l'effet activateur du Pentothal ou d'autres barbituriques à action analogue. Ces publications — et en particulier celles des Gibbs, de Barnes, Bagghi, Epstein and Lennox, Grossman, Merlis, Pampiglione, Passouant pour ne citer que les plus importantes — ont été revues et discutées dans le rapport de Fuster (1953) auquel nous renvoyons. Notre publication se différencie cependant de ces travaux par le souci constant que nous avons eu de situer à la lumière des connaissances neurophysiologiques récentes et dans la mesure de nos moyens, le foyer en regard des structures sous-corticales et des systèmes non-spécifiques éventuellement impliqués dans le processus lésionnel.

*e*) les lésions des noyaux gris centraux s'accompagnent également de bouleversements de ce stade pentothalique; ils s'expriment habituellement par une abolition unilatérale parfois bilatérale de ses activités rapides. C'est également au cours de ces lésions qu'il nous a été donné d'observer des dépressions paroxystiques ipsilatérales et transitoires de l'électrogénèse cérébrale — qui ne peuvent s'expliquer que par l'action dépressive qu'exerce le narcotique sur les centres dyna-

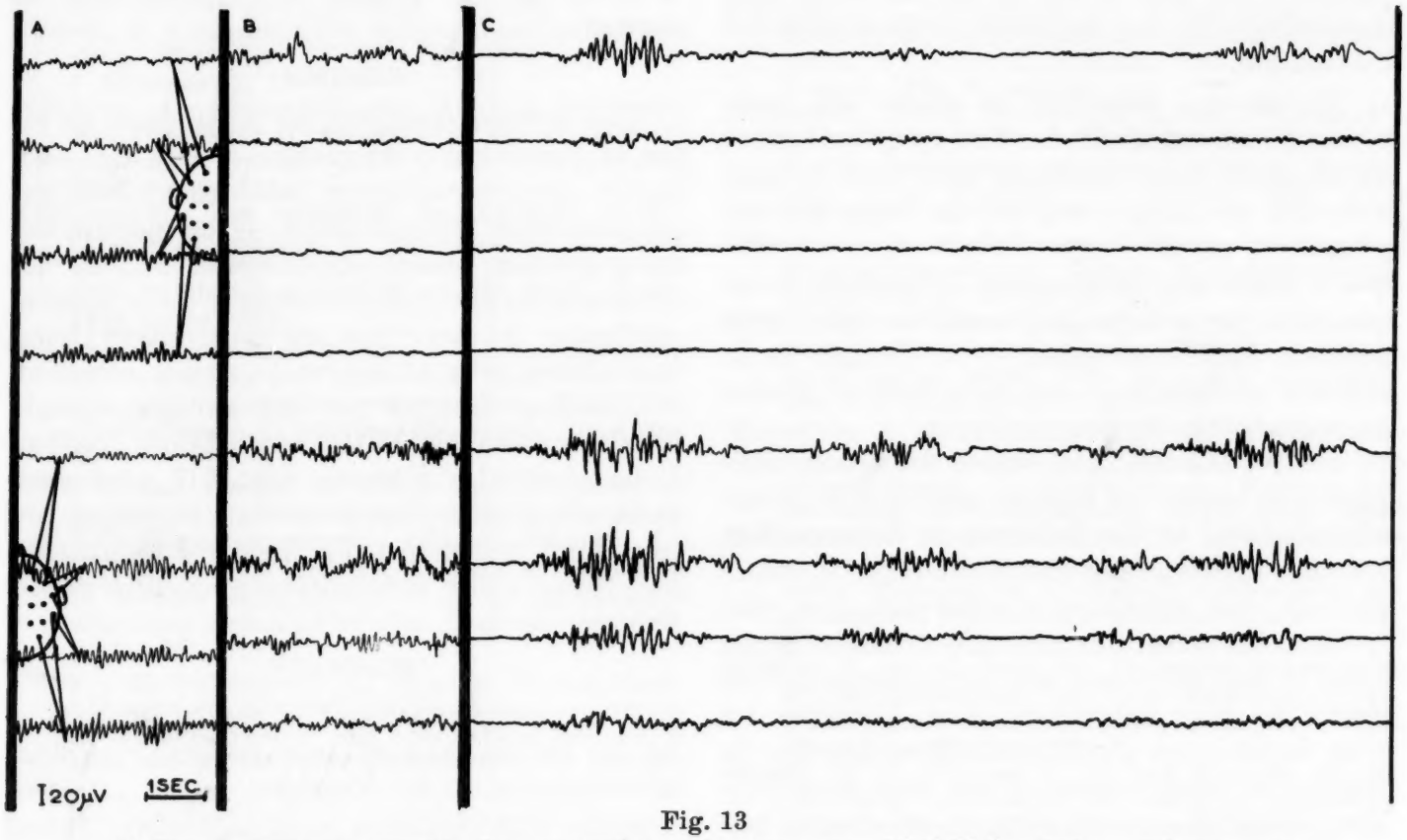


Fig. 13

A) Tracé spontané normal chez un sujet présentant une hémiplégie droite ancienne par hémorragie capsulaire;
B) et C) même sujet sous Pentothal (stades des activités rapides et des complexes-K). A noter les modifications importantes que subissent ces divers stades pentothaliques dont les éléments subsistent uniquement et de façon fruste sur les dérivations antérieures du côté lésé.

mogènes diencéphaliques impliqués dans le processus lésionnel;

*f*) les lésions corticales ou cortico-sous-corticales n'impliquant pas les noyaux gris peuvent aussi influencer ce stade électrographique dans le sens d'une dépression plus ou moins importante de ses éléments — dépression qui cependant restera strictement limitée à l'aire corticale lésée.

Il semble donc que les incitations qui donnent naissance aux activités rapides du stade d'induction anesthésique prennent essentiellement leur départ de la réticulée mésencéphalique. En amont de l'appareil mésencéphalique, ces incitations paraissent cheminer par l'hypothalamus postérieur et le subthalamus pour finalement gagner le cortex en utilisant vraisemblablement les voies thalamique et extra-thalamique décrites par Starzl et Magoun pour la réaction d'éveil (1951). A ce niveau, les incitations semblent surtout utiliser des voies directes, non-croisées; des lésions localisées à la capsule interne et à quelques rares segments antéro-latéraux des noyaux gris centraux (hémorragies dites capsulaires, certains gliomes enregistrés) donnent en effet lieu à des abolitions unilatérales de ce stade électrographique rapide (fig. 13). La capsule interne paraît donc constituer une composante importante de la voie extra-thalamique — et peut-être aussi thalamique — et pourrait être considérée comme une des voies terminales du système afférent. Cette hypo-

thèse semble trouver confirmation dans le travail de Hanbery, Ajmone-Marsan et Dilworth (1954) qui ont montré que les incitations thalamo-corticales non-spécifiques cheminent par la capsule interne. Ces données sont également comparables aux résultats publiés par Epstein et col. (1949) qui ont démontré par des ligatures sylviennes chez le chien anesthésié, que les ''spindles'' du sommeil sont absents lorsque l'infarctus détruit la portion antérieure et moyenne de la capsule interne, la tête du noyau caudé et plus accessoirement les segments antéro-latéraux du thalamus.

En ce qui concerne le stade des complexes-K: il convient de dire que les lésions du tronc cérébral supérieur qui vont de pair avec une abolition complète du stade électrographique rapide, ne modifient en aucune façon le stade des complexes-K. Il semble donc que des structures supra-mésencéphaliques puissent également jouer — à l'image de la réponse secondaire — un rôle dans la genèse de ce complexe électrographique.

Chez l'homme, une lésion du tronc cérébral, une lésion des parties médiales du diencéphale basal ou du thalamus ne donnent lieu à aucun décalage interhémisphérique du complexe-K; ces décalages s'observent par contre dans les affections latérales du diencéphale basal et sont d'autant plus importantes que la lésion est plus antérieure. Les décalages les plus importants s'observent dans les cas de lésions ou compressions d'une aire assez précise, délimitée: *a*) en haut et en avant: par la partie antérieure de la tête du noyau caudé et la partie antérieure de la capsule interne; *b*) plus bas et en avant: par le putamen, le pallidum, la commissure blanche antérieure, l'anse lenticulaire et le genou de la capsule interne; *c*) en arrière: par le noyau subthalamique, les champs de Forel et la zona incerta; *d*) du côté médial: par l'aire pré-optique et le tuber cinereum; et *e*) du côté latéral: par les structures hippocampique et amygdalienne et la queue du noyau caudé.

La capsule interne nous semble finalement constituer la voie terminale du complexe-K et sa lésion provoque une abolition homolatérale presque complète de ce complexe électrographique (fig. 13). La voie d'acheminement du complexe-K pourrait donc correspondre de très près à la voie extra-thalamique suggérée par Dempsey-Morison (1941) pour la réponse secondaire et décrite par Starzl et Magoun (1951) pour la réaction d'éveil.

Méthode dynamique dont on sait diriger l'évolution suivant les suspicions cliniques et les exigences de l'examen, la technique pentothalique permet ainsi une véritable exploration cortico-sous-corticale et peut de ce fait jouer un rôle essentiel dans la focalisation électrographique précise d'un processus lésionnel.

RÉSUMÉ

Les auteurs discutent les possibilités qu'offre le Pentothal pour mettre à jour des anomalies électrographiques latentes et localiser un processus intra-crânien — en particulier un processus lésant ou comprimant: *a*) les centres sous-corticaux réglant l'électrogénèse cérébrale; *b*) les voies qu'empruntent leurs incitations pour atteindre le cortex cérébral.

Résultat fournis par les enregistrements sous Pentothal de 360 sujets atteints d'affections cérébrales diverses dont 117 néoformations auxquelles l'intervention, l'autopsie ou les techniques neuro-chirurgicales habituelles ont apporté une focalisation particulièrement précise.

SUMMARY

The authors discuss the possibilities offered by the method of intravenous Pentothal administration to disclose latent electrographic abnormalities and to localize intracranial lesions, in particular those involving (*a*) the subcortical structures regulating the ''cerebral electrogenesis'' and/or (*b*) the pathways connecting these structures with the cerebral cortex. These lesions may either involve subcortical areas directly or indirectly by pressure exerted upon them by a more distant lesion.

The authors present the results obtained in records taken under Pentothal in 360 patients suffering from various cerebral lesions, among which were 117 with neoplasms, in which a particularly exact location of the lesion was ascertained either during surgical intervention, by autopsy or by one of the usual neuro-surgical diagnostic procedures.

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# *ANNOUNCEMENT*

## PREMIER CONGRÈS INTERNATIONAL DE SCIENCES NEUROLOGIQUES
### BRUXELLES 1957
### Renseignements préliminaires

Tenant compte de la décision de l'assemblée générale de la Fédération Internationale des Sociétés EEG et de Neurophysiologie clinique à l'issue de son IIIe Congrès à Boston, le Comité d'organisation de notre IVe Congrès International a décidé de tenir ses assises, conjointement avec le congrès international de Neurologie, en 1957 à Bruxelles, le 21-28 juillet.

L'appellation globale du Congrès sera la suivante: ''Premier Congrès International des Sciences Neurologiques''. En sous-titre : VIe Congrès International de Neurologie, IVe Congrès International d'EEG et de Neurophysiologie Clinique, IIIe Congrès International de Neuropathologie, 1er Congrès International de Neurochirurgie, Ve Réunion de la Ligue Internationale contre l'Epilepsie et Ve Symposium Neuroradiologique.

***Comité d'organisation du Congrès :***

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L'ensemble du Congrès s'échelonnera sur les six jours ouvrables d'une semaine. Le dimanche *précédent* comportera le matin, la réunion de la Ligue Internationale contre l'Epilepsie et l'après-midi la séance générale d'ouverture avec la soirée de réception.

La matinée du dimanche *suivant* sera consacrée aux réunions administratives privées des diverses disciplines réunies en congrès. Celles-ci seront suivies d'une Réunion Générale de tous les délégués, qui statuera, d'après l'expérience acquise et les désirs des assemblées particulières, de la forme et des modalités des Congrès internationaux futurs.

Le partage du temps se fera de façon strictement égale, de même dans la limite du possible pour la participation aux thèmes généraux acceptés à la majorité pour les deux journées communes.

Ce sont: 1. La pathologie extrapyramidale.
2. Signification et interprétation des modifications de la Conscience.

***Thèmes choisis (EEG) pour les quatre jours suivants :***

1. Interprétation du potentiel musculaire normal et pathologique:
   *a*) Les paramètres et patterns de l'unité motrice.
   *b*) Physiopathologie des méchanismes centraux.
   *c*) Physiopathologie des méchanismes neuro-musculaires.
2. L'EEG dans le comportement conditionné.
3. Les ''anomalies'' électroencéphalographiques comme signes de la pathologie cérébrale.
4. Symposium sur la pathogénie et la clinique du Petit Mal épileptique.
5. Symposium sur l'Evolution ontogénique de l'EEG.

La décision de publication intégrale avec *précirculation* des rapports et des communications libres exigera leur envoi au Comité coordonné d'organisation du Congrès, *au plus tard, pour le 1 février 1957*. Une communication libre ne pourra fatalement être inscrite que lorsque son auteur aura acquitté son droit d'inscription au Congrès.

Afin d'assurer la bonne marche de nos réunions avec la plus large diffusion et discussion possible, le comité suggère une sélection des communications par les sociétés nationales elles-mêmes. Chaque participant a droit à une seule communication libre, qu'elle soit signée par l'auteur seul ou en collaboration. Notre comité organisateur choisira les mesures les plus efficaces pour rendre aux communications libres leur intérêt actuellement très contesté par la majorité. Celles-ci vous seront communiquées ultérieurement.

Le droit d'inscription à l'ensemble du Congrès international des Sciences Neurologiques sera de 15 dollars par participant, membre titulaire d'une de nos sociétés respectives, de 10 dollars pour les membres associés (médecins ou scientistes s'intéressant à la neurologie) et de 5 dollars pour les membres adjoints (non-médecins s'intéressant au Congrès).

Au même titre que les sociétés nationales de Neurologie, de Neurochirurgie et de Neuropathologie, les diverses sociétés EEG nationales contribueront aux frais d'organisation du Congrès. Les Sociétés de Neurologie et de Neurochirurgie ont accepté le principe du prix forfaitaire de *un* dollar par membre et par année de 1955 à 1957, soit *deux dollars par membre affilié*. En cas d'impossibilité matérielle, nous sommes convaincus que nos sociétés nationales d'EEG verseront au moins une contribution financière en rapport avec leurs moyens et leur importance numérique. La participation au banquet de clôture devra être signalée au moment de l'inscription au Congrès et la redevance versée avec le droit d'inscription.

Les rapports et les communications libres seront publiés en français ou en anglais. Pour l'exposé oral des travaux, le principe de l'égalité des langues a été admis. Néanmoins, le désir d'être compris par le plus grand nombre possible d'auditeurs réduira nécessairement le nombre des langues à employer. Le comité organisateur envisage dès maintenant la possibilité de traduction simultanée pour l'anglais, le français et l'allemand. Pour tout exposé dans une autre langue, l'auteur est invité d'en remettre une traduction fidèle dans une des trois langues officielles (français, anglais ou allemand) et ce en trois exemplaires, pour permettre la traduction simultanée.

Agences de Voyages officielles: The American Express Company and Thomas Cook & Son.

# SURFACE AND DEPTH ELECTROGRAPHY OF THE FRONTAL LOBES IN CONSCIOUS PATIENTS [1]

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Experimental implantation of electrodes in the brain of different species of animals has been repeatedly done in the last fifty years. (See bibliography in Delgado 1952, 1955.) In human patients, direct recording of the exposed brain and of its depth has been used by several neurosurgeons, mainly for exploration in epilepsy and tumors (Hayne *et al.* 1949; Jung and Kornmüller 1938; Kirikae *et al.* 1953; Meyers *et al.* 1949; Okuma *et al.* 1954; Penfield and Jasper 1947; Scarff and Rahm 1941; Spiegel and Wycis 1950; Walter and Dovey 1946; Williams and Parsons-Smith 1949; Wycis *et al.* 1949). Some techniques have been recently developed to implace electrodes in the human brain for longer periods — days or even months in some cases (Brazier *et al.* 1954; Delgado *et al.* 1952; Dodge *et al.* 1953; Heath 1954). The aims in implanting electrodes in the human brain may be summarized as follows: (*a*) to explore the brain in certain epileptic patients through a small burr hole in order to facilitate diagnosis and to direct surgery. This exploration may be less traumatic than the open method, with the added advantage that there is no pressure of time and recordings and stimulations may be repeated during several days (Delgado 1956); (*b*) to electrocoagulate small areas of the brain, selected after functional exploration (Hamlin *et al.* 1953). Some basis for this procedure derived from the present trend to find therapies more conservative than radical lobotomy (Fulton 1951; Grantham 1951; Mandl 1951) and from animal experimentation, which showed it was possible to produce lobotomy symptoms after small and selective electrocoagulations in the neighborhood of the head of the caudate nucleus (Delgado and Rosvold 1953; Rosvold and Delgado 1956); (*c*) to apply electrical stimulation to selected areas of the brain for prolonged periods, attempting a therapeutic benefit (Heath 1954). In any case, the implanting of electrodes offers exceptional opportunity to obtain direct recording of various areas of the brain without the influence of anesthesia, sedatives, surgical trauma or psychological stress. Criticisms against electrode implantation have been expressed by some authors (e.g. Lilly 1954). The electrical activity of the depth of the frontal lobes has been studied by Sem-Jacobsen *et al.* (1953, 1955), by Delgado *et al.* (1953) and by Delgado and Hamlin (1954). The work of Heath's group (1954) has been mainly concerned with the septal area.

In this paper we present data of electrical activity obtained in 9 patients in whom depth electrodes (multilead needles) were placed in comparable areas of the frontal lobes. Additional information was obtained in 4 of these patients from surface electrodes (multilead plates) placed over the convexity of the frontal area.

*Subjects.* Five cases of schizophrenia, 3 of intractable pain, and one of anxiety neurosis were studied. All the patients, including the schizophrenics, were in good contact and none of them except one had records of epileptic attacks. As shown in table I, some had and some had not had electroshock therapy. In any case, the electroshocks had been discontinued at least one year previous to electrode implantation. Lobotomy had been advised in all cases, and implantation of electrodes and focal

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electrocoagulation was used as an alternative procedure. Explicit written consent for electrode implantation was obtained in all the pain and anxiety cases from the patient himself, and in schizophrenics, from the families.

The electrodes were left in the brain the minimum time necessary for functional exploration and electrocoagulation. In general, 2 and a half days sufficed. In one case 4 days were necessary; in another, operated under local anesthesia, only 24 hours were required.

Data concerning each patient follows:

*Patient No. 1.* W. S. Male. 50 years old. Diagnosis of Tabes Dorsalis made in 1935 when he became atoxic, stumbled and fractured his ankle. Tabetic colloidal gold curve. From 1941-45 numerous gastric crises. Neuropathic joint of Charcot type. In July, 1952, because of persistence of intractable root pain and the failure of narcotics to properly control this condition, lobotomy was advised. Neurological findings included sluggish reactions of the pupils to light, optic atrophy of the left disc with some atrophy of the right, diminution of vibratory senses on the right, markedly impaired position sense of the extremities, cutaneous sensibility of both lower extremities to the knees, passed pointing finger to nose, absent reflexes of lower extremities.

Spinal fluid examination, however, showed negative Wassermann, total protein was 39 mg. per cent, colloidal gold 110000000. Blood Wassermann was negative.

Patient was well oriented in all spheres. Recent and remote memory intact. Retention and recall was slow. Intellectual capacity was below average. *Scalp EEG*: basic pattern of low to moderate 9-10 sec. activity posteriorly dominant. Anterior much low voltage fast activity occurred. In hyperventilations no significant changes. Impressions: Normal alpha recording.

*Patient No. 2.* A. N. Female. 39 years old. Diagnosis: Schizophrenia, Hebephrenic. Onset of illness at the age of 36 (1949). Withdrawal, autistic thinking, auditory hallucinations, thought nobody cared for her. Vague, circumstantial grimacing. Inappropiate laughing and giggling. Crying spells. Occasional episodes of hostility. Electroshock in 1949, 1950 and 1951. Insulin in 1949 and 1950. *Scalp EEG*: flat, regular activity about 9 c/sec. in all channels with runs of higher amplitude at occipital leads.

*Patient No. 3.* F. G. Male. 49 years old. Diagnosis: Schizophrenia. Undetermined type. Onset of illness at the age of 24. Afraid of dying. Suicide attempt at the age of 27 by cutting throat. Preoccupied, sullen, rigid emotionally, felt that he was to be killed. Auditory hallucinations. Since 1936 emotionally flat, preoccupied, speech disconnected, mumbled to himself, dishevelled, repeated attempts to elope. *Scalp EEG*: flat irregular activity of changing frequency between 6-15 c/sec. Short bursts of about 22 c/sec., 40 $\mu$V. in the right parietal regions.

*Patient No. 4.* I. P. Female. 35 years old. Diagnosis: Schizophrenia hebephrenic. Onset of illness at the age of 20 (1938), after a failure in a love affair. Patient believed that people were talking about her, and that everything in the house was picked up by wires, radio, and television. Would sit and stare. Inappropriate emotionally, giggling and laughing one day, fighting the next. Somewhat incoherent in her speech. Assaultiveness and withdrawal were the most prominent features. Metrazol therapy in 1940. Electroshock in 1951. *Scalp EEG*: flat activity, regular, about 10 c/sec.

*Patient No. 5.* J. B. Female, 30 years old. Diagnosis: Schizophrenia hebephrenic. The patient had convulsions and fainting spells when 2 years of age. She received 7 electroshocks at the age of 3. Onset of illness at the age of 22 (1946). Fear of being stabbed, heard voices, behavior silly, sullen, irritable, much giggling, unpredictable aggressiveness. Feelings of unreality and depersonalization. Elopement attempts. Electroshock therapy in 1948 and 1950. *Scalp EEG*: very flat activity in the frontal leads. Considerable amount of muscle artefact in the temporal and occipital regions.

*Patient No. 6.* H. G. Male. 52 years old. Diagnosis: Thalamic pain. Onset of illness at the age of 50 (1951). The patient had a stroke in which the right side was paralyzed and he was not able to talk. He recovered motion soon, first in legs, then in the arms. He started making sounds the 3rd day after the stroke. He recovered speech gradually and two months later the stroke pains started, first in the fingers of right hand then spread throughout the body, causing great suffering. The pain in the throat was the main complaint. Patient very tense and rather emotional. *Scalp EEG*: 8-9 per sec. alpha activity predominated in all areas. No bilateral differences noted. EEG normal.

*Patient No. 7.* C. H. Female. 32 years old. Diagnosis: Schizophrenia, undetermined type. Onset of illness at the age of 26 following birth of third child. Irritable, sleepless, resented having children. Picked up by police. Vague, seclusive, retarded, some blocking, dilapidated in personal appearance. Verbal improductiveness, inappropriate laughter, unpredictable assaultive behavior. Electroshock therapy in 1947, 1950, and 1951. Insulin coma in 1950.

*Patient No. 8.* Female. 36 years old. Diagnosis: Obsessive compulsive reaction. Onset of illness at the

age of 34 (1951). Following automobile accident she became progressively worried about her health. Became depressed and disinterested, pains in her back. Fear of picking up germs. Would not touch a paper in which the word "polio" appeared or where the letters T and B were too close together. Excessive hand washing, would not touch anything that had been on the floor. Electroshock therapy in 1952. *Scalp EEG*: stable 10-11 sec. activity seen in the occiput bilaterally and was present at lower voltage and in shorter runs anteriorly. Very rarely, frontal activity became a little more irregular than that of other areas for about one sec. Tracings fall within normal limits.

*Patient No. 9.* W. E. Male. 58 years old. Diagnosis: Tabes Dorsalis. For the past 12 years has had severe shooting pains in the lower extremities. The pain occurred anywhere from the hips on down, and in spells. The spells might last for several days and they incapacitated the patient. He was unable to sleep and required morphine. In addition, the patient had difficulty in walking. Within the past year, the pain became so intense that the patient was no longer able to work. Intellectual functioning on structured tasks requiring the integration of well-learned skills retained. However, there were signs of loss of intellectual competence in unstructured learning situations. The various visual-motor tasks revealed considerable loss of capacity especially when a time element was introduced.

## METHOD

Description of method for construction and implantation of electrodes in animals (Delgado 1955) and in human patients (Delgado, Hamlin and Chapman 1952) has been published elsewhere. A short summary is given here. Needle electrodes to explore the depth of the frontal lobes were made of 7 silver wires, .1 mm. in diameter, covered with quadruple teflon. The contacts of each of the 7 wires (4 mm. scraped bare of insulation) were spaced at 8 mm. intervals. The 7 leads were cemented together with plexiglas dissolved in dichloroethylene and soldered in an identifiable order to a 7 pin subminiature radio tube socket. The diameter of the 7 leads together was about .5 mm. This electrode was rather soft, but had the advantage that it followed any brain movement, thus minimizing trauma and artefacts. A rigid stainless steel tube, .3 mm. in diameter, was used to introduce the needle electrode into the brain. A hook at the tip of the electrode was caught on the tip of the introducer and they were held together by a small arterial clamp. The needle was inserted to the desired depth with the upper contact No. 7 at the level of the cortical surface. Then the clamp was removed, the silver wires were adapted to the edges of the burr hole by passing a small loop between bone and dura, and the introducer was pulled out, leaving the electrode within the brain. The plate electrodes for surface recording were made of 7 leads of teflon-insulated silver wire, and encased in 1 mill polyethylene sheet, with small silver balls, .5 or 1 cm. apart, protruding from one side of the plate. The other end of the leads was soldered to a subminiature radio tube socket. Needle and plate electrodes were implaced in the brain through 2 cm. burr holes made with the patient under Pentothal-nitrous oxide general anesthesia. In one case, shown in table I, local anesthesia was used. The needle electrodes were sterilized by autoclaving; the plate electrodes by immersion in 1:1000 Zephiran solution for 12-16 hours. Both plate and needle electrodes were fixed to the scalp with one silk suture and the small sockets taped to the dressing. When the patients wakened from anesthesia lateral and anteroposterior X-rays of the skull were obtained to check the position of the leads. After the observation period the stitch which fixed the electrode to the scalp was cut and the electrodes removed by gentle pulling, a procedure well tolerated by the patient. As the silver wire at the tip of the needle electrode was soft, the hook opened as the electrode was withdrawn, thus minimizing damage. Recording equipment included a Grass stimulator model S-44, a DuMont dual beam oscilloscope type 321, an 8 channel Grass electroencephalograph model III D, a tape recorder, and still and motion picture cameras.

## RESULTS

Implantation of electrodes proved to be safe in all the patients. Electrocoagulations were also uneventful. No deficit of any kind resulting from the operation could be observed after the electrocoagulation. None has had seizures in the follow-up period of up to

three years. Improvement in the schizophrenics, apart from that which could be explained by greater attention paid to them, was doubtful. Two of the three patients with intractable pain had transitory improvement.

*Location of electrodes.* The approximate location of the leads was estimated in the X-ray films (fig. 1). Transparency drawings of X-rays of all cases showing the position of the electrodes are seen in figure 2. Patients 2, 3, 4 and 5 had 2 plate electrodes, represented by the 2 more posterior lines in the anteroposterior tracings, which covered premotor and motor areas. The position of these plates was comparable in patients 2, 3 and 4, and more inferior in patient 5. In addition, all these patients had two needle electrodes within the frontal lobes. The most caudal needle was placed in patient 8, and was probably at about the plane of the anterior commissure. The most anterior electrode was placed in patient 9, and was probably in the white substance of the frontal lobe. Leads very close to the midline were placed in patients 7, 8 and 9; leads about equidistant from the external surface and the midline were placed in patient 6. Within the limits mentioned the following structures could be principally involved: frontal cortex, tip of the temporal lobe, white substance of the frontal lobes, corpus callosum, lateral ventricle, septal area, corpus striatum.

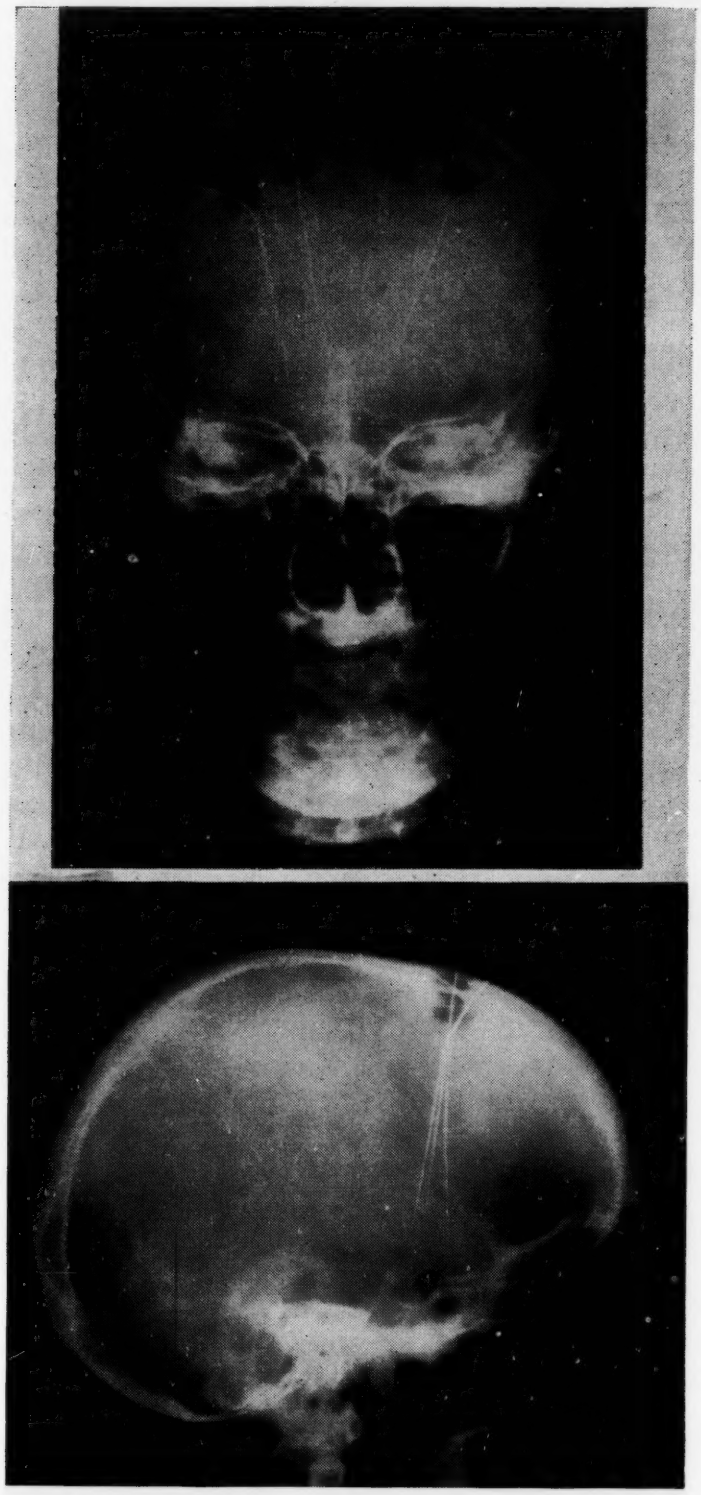

Fig. 1

X-rays of patient 8 showing 4 needle electrodes implanted within the frontal lobes.

*Typical patterns of activity.* Some patterns of electrical activity have been repeatedly observed in recordings taken from different patients and a description of them follows:

1. Low voltage activity characterized by amplitude below 50 $\mu$V. and frequency about 7-14 c/sec. This was commonly observed in the deep part of the frontal lobes close to the midline, more rarely at the surface. Sometimes low voltage activity was present at several depths with about the same amplitude, while in other cases there was an increase of amplitude from depth to surface. Recordings of flat activity with high amplification showed patterns which, in some cases, were independent of those recorded through the neighboring leads, suggesting some independence of source. More often, however, low voltage activity in the depth had a similar frequency to that of the more superficial areas.

2. Alpha-like activity, characterized by waves of medium amplitude of about 50 $\mu$V. and dominant frequencies of about 8-13 c/sec., was recorded more often from the depth than the surface of the frontal lobes, and in some patients it was not observed at all.

3. High voltage fast activity characterized by amplitude up to 250 $\mu$V. and a dominant frequency of 12-30 c/sec., usually mixed with some slower waves and spiky activity, was observed in the precentral cortex (recorded by plate electrodes) and also in the more lateral part of the depth of the frontal lobes (recorded by needle electrodes). Often bursts of increased amplitude were recorded simultaneously in several channels. This type of activity is known to be typical of Pentothal anesthesia (Brazier and Finesinger 1945) and has been recorded from surface and depth of the frontal lobes for periods up to two

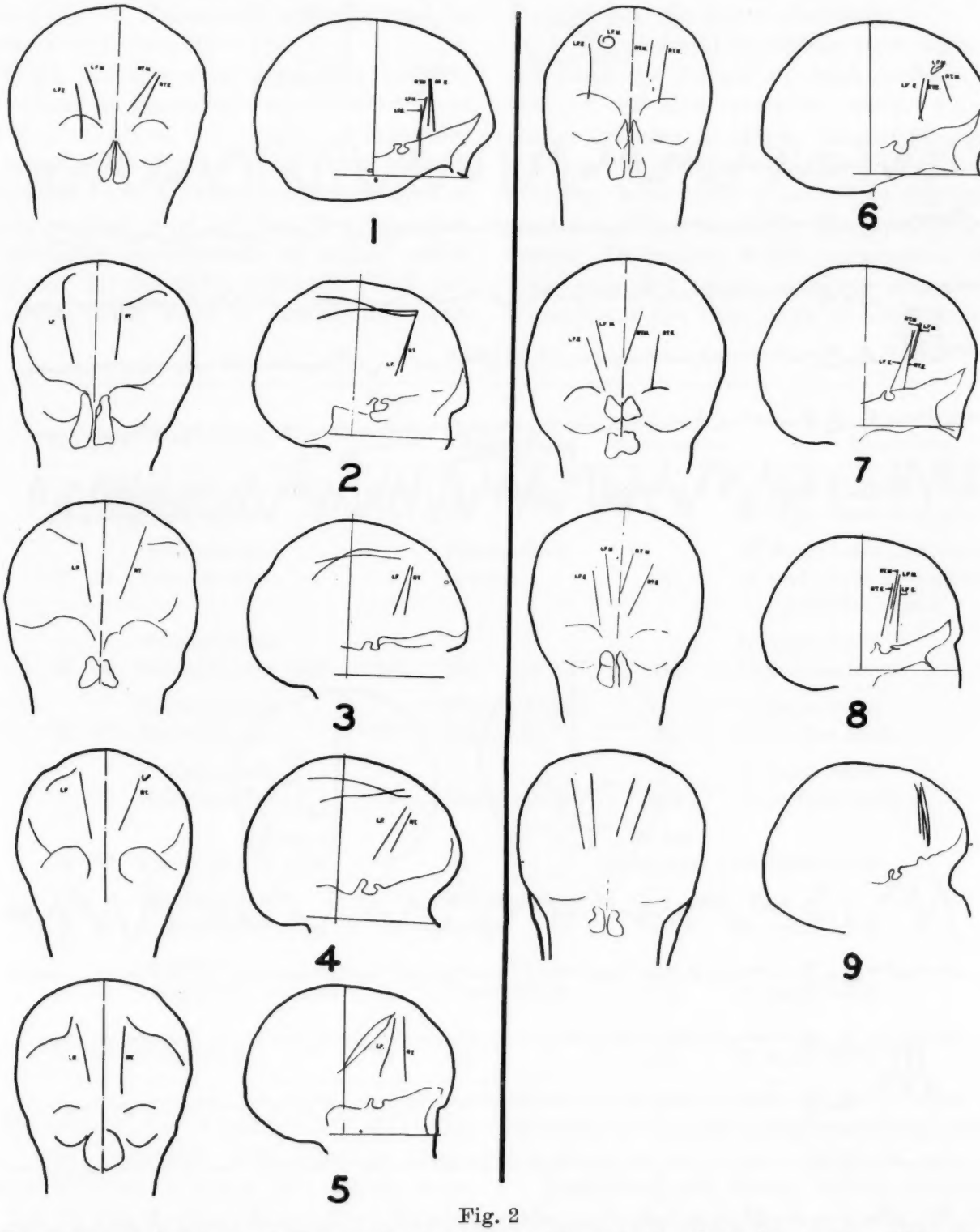


Fig. 2
Transparency drawings of X-rays showing the position of the electrodes in the different patients.

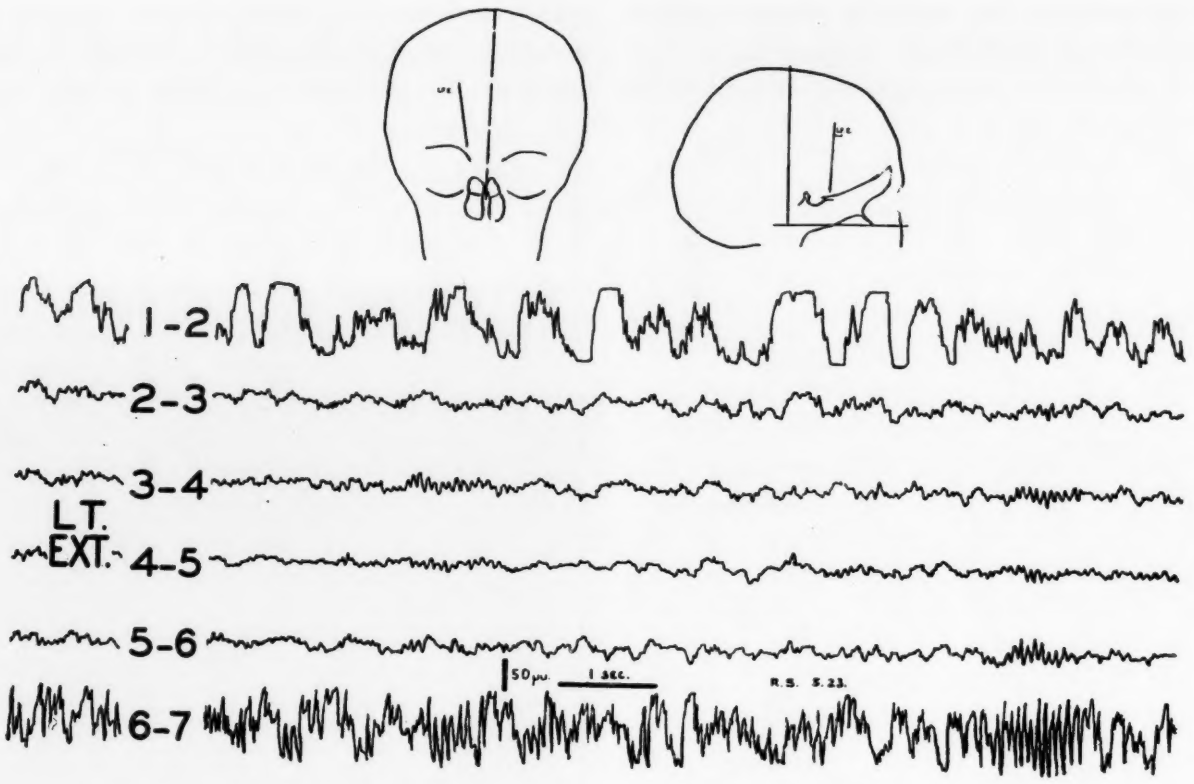


Fig. 3

Distribution of rhythms in depth may be similar in different patients. Recordings taken 2 days after the operation. Compare with LFT MD in fig. 5. *Note for this and all following figures*: Contacts 1 or 11 are at the tip. Contacts 7 or 17 are at the base of the electrodes. All recordings were bipolar.

days after the operation (Brazier *et al.* 1954). In those rather rare subjects whose spontaneous rhythm is in approximately the same frequency band, Pentothal activity may be difficult to differentiate.

4. High voltage slow irregular activity characterized by amplitude up to 300 $\mu$V. of slow waves of about 2-5 c/sec., of irregular shape mixed with fast activity: this pattern was recorded from a rather restricted area in the ventromedial part of the frontal lobes, which probably corresponds to septal nuclei or striatum. In the three patients (1, 7 and 8) in whom leads were in comparable locations (see table I, fig. 3 and 5 LFT MD) the activity was recorded with similar characteristics through linkages 1-2, which were at the tip of the needle electrodes. The described activity was absent in the other leads of the same patients and in the rest of the group. It must be emphasized that the diagnosis of these three patients was different, suggesting that there is no correlation between the high voltage slow irregular activity and the type of illness. A similar type of activity at some points of the orbital surface of the frontal lobes has also been observed in another group of schizophrenic patients, recorded through plate electrodes.

5. Paroxysmal rhythmic slow waves characterized by bursts of high voltage up to 300 $\mu$V of slow activity, about 4-5 c/sec., rather regular in shape, amplitude and frequency, alternating with faster spiky irregular activity, have been observed at the most superficial point, probably corresponding to the cortex. In patient 1 this paroxysmal activity was recorded with similar characteristics throughout the four days of observation. No relation to clinical symptomatology could be found.

6. Spikes and sharp waves, isolated and also in runs, have been seen from time to time at different depths of the frontal lobes in all the patients studied. Examples of spiky activity and sharp waves are shown in figure 4. The activity, however, was far less striking than that recorded in a group of epileptic patients.

7. A mixture of the patterns described

TABLE I

| *Patient* | *Sex* | *Age* | *Diagnosis* | *Years of illness* | *Electroshock* | *Days of implantation* | *Electrodes* |
|---|---|---|---|---|---|---|---|
| 1<br>W S | M | 50 | Taboparesis | 15 | No | 4 | 28 depth leads in frontal lobes |
| 2<br>A N | F | 39 | Schizophrenia<br>Hebephrenic | 5 | Electroshock<br>Insulin | 2½ | 14 depth leads in frontal lobes<br>14 surf. leads over motor, premotor cortex |
| 3<br>F G | M | 49 | Schizophrenia<br>undetermined type | 24 | No | 2½ | 14 depth leads<br>14 surface leads |
| 4<br>I P | F | 35 | Schizophrenia<br>Hebephrenic | 15 | Electroshock<br>Metrazol | 2½ | 14 depth leads<br>14 surface leads |
| 5<br>J B | F | 30 | Schizophrenia<br>Hebephrenic | 8 | Electroshock | 2½ | 14 depth leads<br>14 surface leads |
| 6<br>H G | M | 52 | Thalamic (?) pain | 2 | No | 24 hrs (local anes.) | 28 depth leads |
| 7<br>C H | F | 32 | Schizophrenia<br>undetermined type | 6 | Electroshock<br>Insulin | 2½ | 28 depth leads |
| 8<br>R S | F | 36 | Obsessive<br>Compulsive reaction | 2 | Electroshock | 2½ | 28 depth leads |
| 9<br>W E | M | 58 | Taboparesis | 12 | No | 2½ | 28 depth leads |

above and other types of activity more difficult to classify have also been observed.

*Correlations among patterns of activity.* In some patients the electrical activity recorded at different depths of the frontal lobes showed an increase of amplitude from depth to surface with a close correlation of frequency and shape of waves, as shown in figure 4 RT. The greatest amplitude did not generally correspond to the most superficial point but to linkages placed 8 to 16 mm. below the cortical surface, with reversals at this level. Linkage 5-6 may be compared with linkages 4-5 and 6-7 in figure 4 RT. More often, however, we have observed abrupt changes in the electrical activity of points only a few millimeters apart. In figure 5 for example, quite different types of activity appeared in LFT MD 11-12, 12-13, 16-17 and LFT EXT 1-2, 2-3, suggesting a local autonomy in the origin of the waves. Tape recordings of interviews synchronized with electroencephalographic recordings failed to show mutual correlations. The patients were silent, talkative, laughing, relaxed or emotionally excited without observable modification of the electrical activity. Opening or closing the eyes, which usually influences the occipital alpha activity, did not change the electrical activity of the frontal lobes. Movements of the limbs and changes in the position of the patient did not affect the recordings.

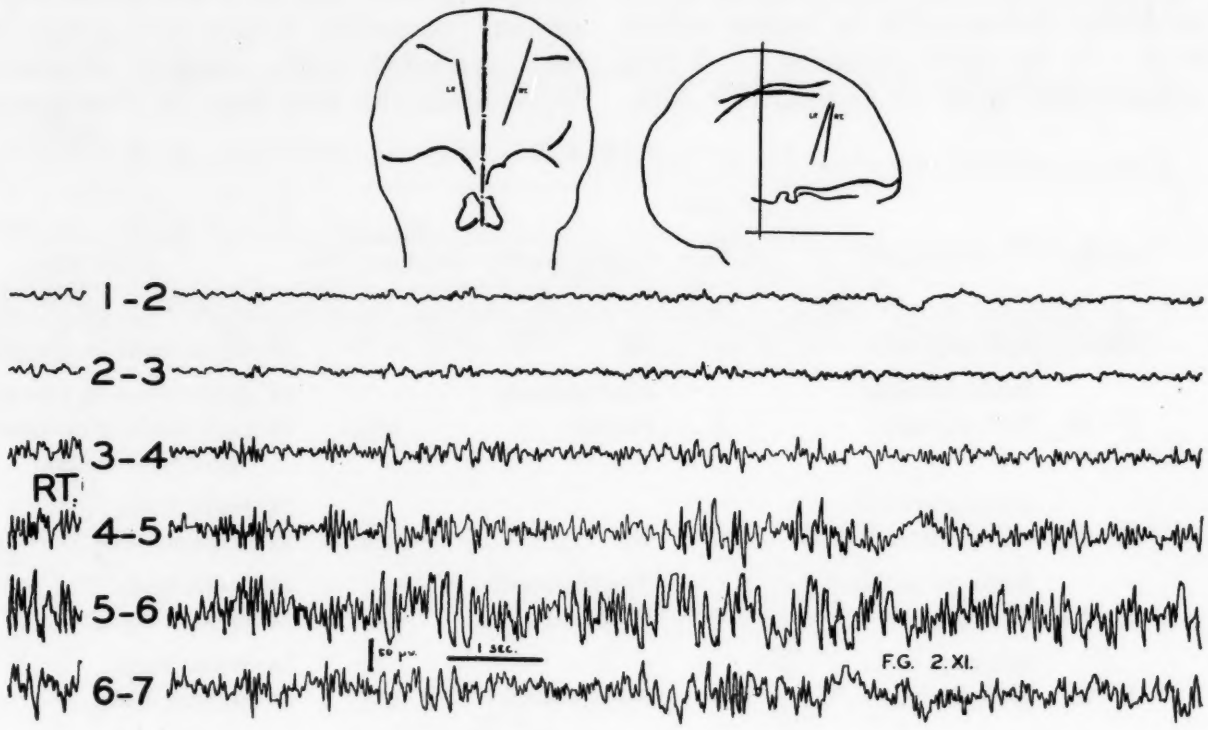


Fig. 4

Electrical activity was generally symmetrical in both frontal lobes. There were exceptions as shown in the next figure. Recordings taken 2 days after the operation.

*Spatial distribution of rhythm.* As the interelectrode distance in each needle was constant, samples of electrical activity at different depths and the spatial distribution of these rhythms could readily be compared. As shown in figure 2 the electrode RT EXT of patient 7 was in a similar position to the electrode LFT EXT of patient 8, and as shown in figure 3, the electrical activity was

Fig. 5

Electrical activity recorded through 4 needle electrodes in patient 1, three days after implantation. Gain was reduced in LFT EXT as shown by the calibrations. See text for explanation.

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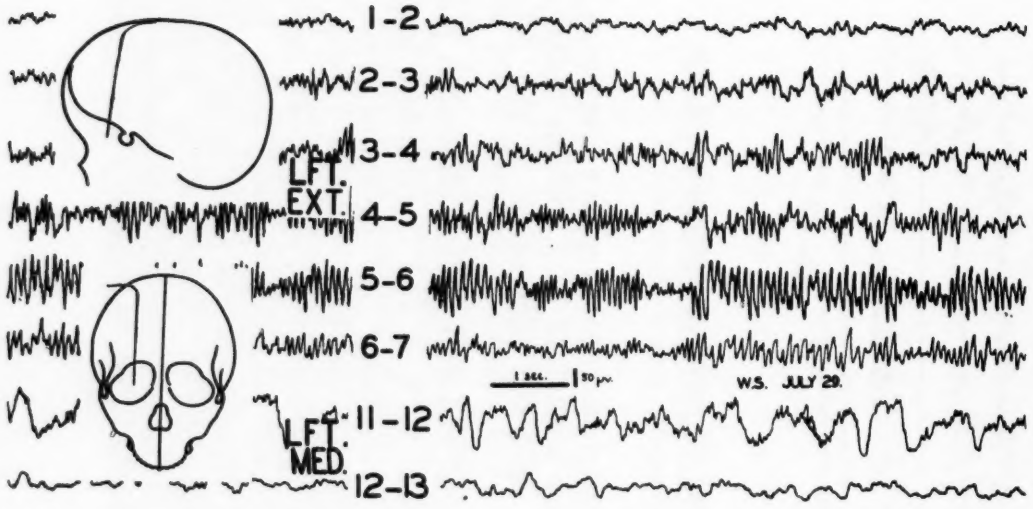
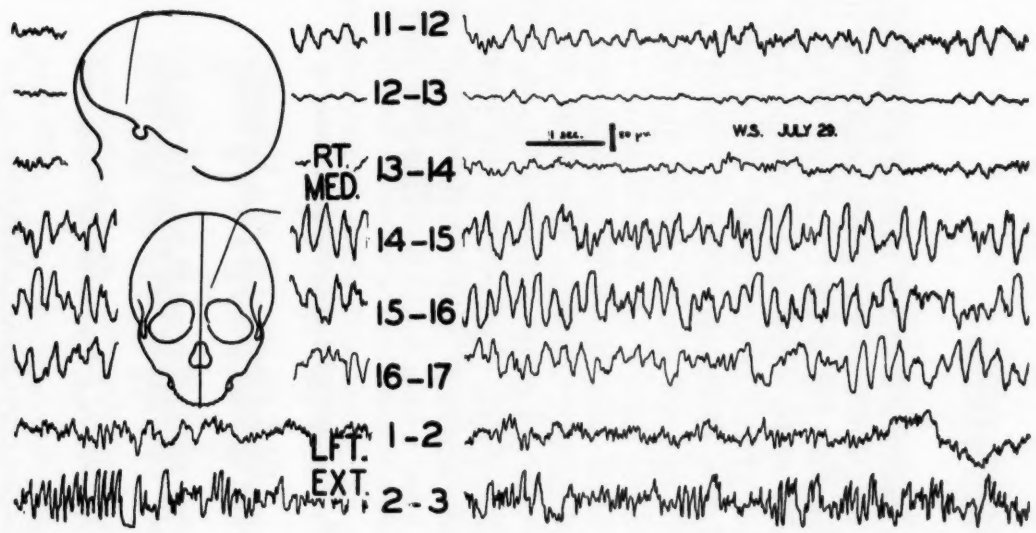
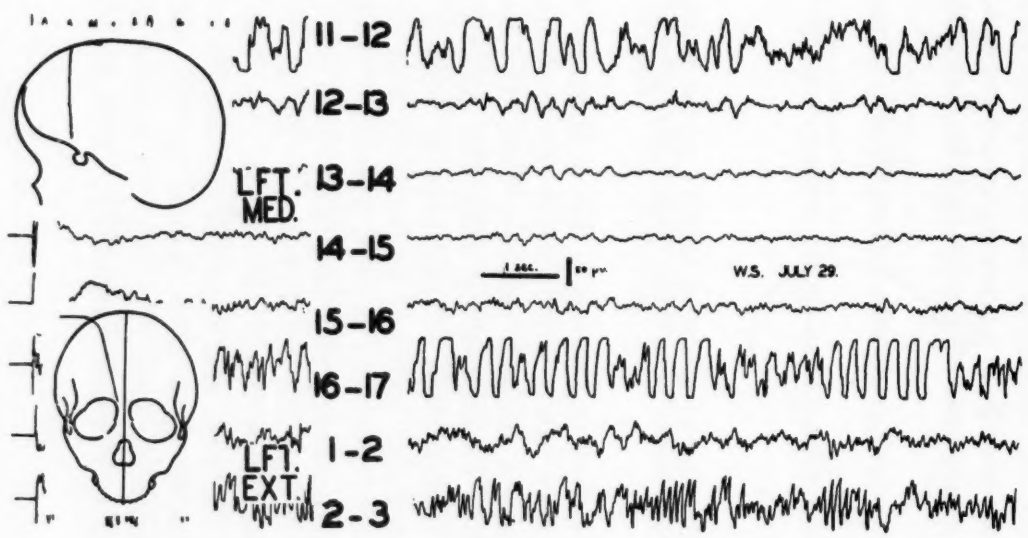

1-2
2-3
3-4
LFT. EXT.
4-5
5-6
6-7
1 sec.
50 μv
W.S. JULY 29.
11-12
LFT. MED.
12-13

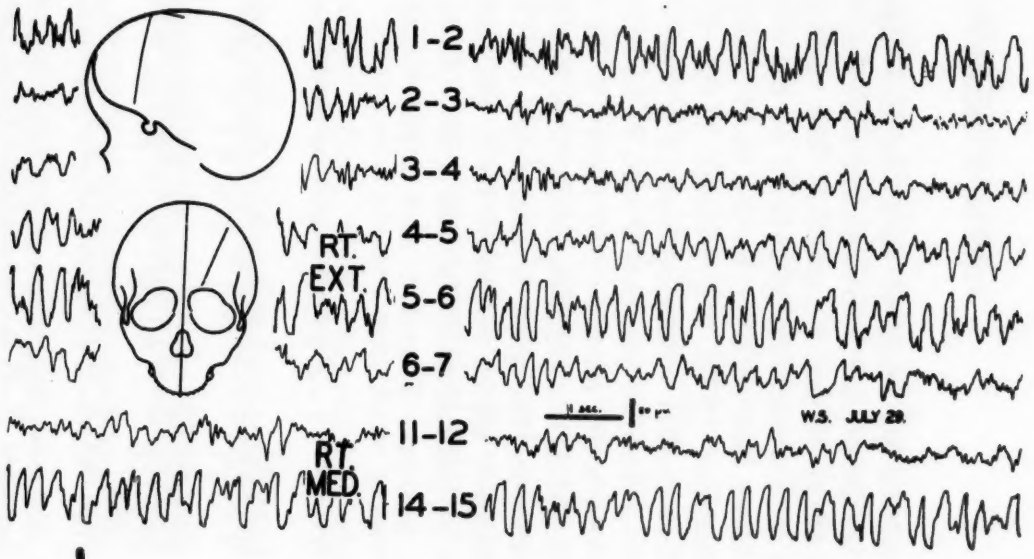
a.


11-12
12-13
1 sec.
100 μv
W.S. JULY 29.
RT. MED.
13-14
14-15
15-16
16-17
1-2
LFT. EXT.
2-3

c.


11-12
12-13
LFT. MED.
13-14
14-15
1 sec.
100 μv
W.S. JULY 29.
15-16
16-17
1-2
LFT. EXT.
2-3

b.


1-2
2-3
3-4
RT. EXT.
4-5
5-6
6-7
1 sec.
100 μv
W.S. JULY 29.
11-12
RT. MED.
14-15

d.

alike in both patients at each depth: high voltage irregular slow waves mixed with faster activity at the deepest point (1-2), low voltage activity at intermediary points (2 to 6), and high voltage fast activity at the most superficial linkages (6-7). In patient 1 the tip of the left medial electrode was in a similar location to those in patients 7 and 8, and the top a little more anterior; in figure 5 LFT MD the spatial distribution of rhythm is also comparable in the first 5 channels. In the sixth channel, which recorded from the most superficial points, activity was high voltage fast in patients 7 and 8 and high voltage EXT in patients 1 and 6, alpha-like and high voltage fast activity was predominant at different depths (fig. 5 LFT EXT). When the needle electrodes were almost symmetrical in both sides of the frontal lobes, as in patients 2 and 3, the electrical activity proved to be similar in pattern and in spatial distribution, as shown in figure 4. Simultaneous recordings of both sides failed to demonstrate complete synchrony, showing that the electrical activity has a partial independence in either side. In one case (patient 1) the pattern of electrical activity was different in each frontal lobe, which could be caused in part by

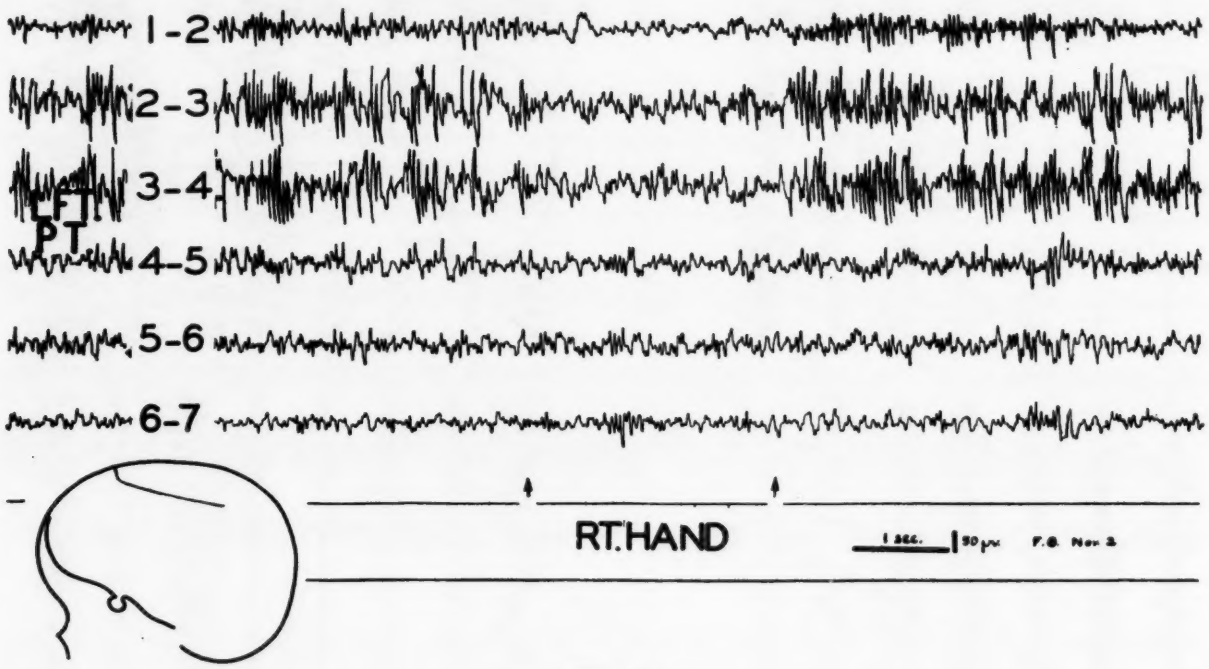



Fig. 6

Blocking of electrical activity of the motor area determined by voluntary contraction of the right hand. Recordings taken 2 days after the operation.

rhythmic slow in patient 1. Recordings in the figures were taken 2 days after the operation. Diagnoses in these 3 patients were different (see table I) suggesting that the described similar distribution of rhythms is related to the anatomical location of contacts and does not depend upon the type of illness. The spatial distribution of rhythms most often recorded through needle electrodes close to the midline was low voltage activity in the 3 or 4 deepest contacts, and high voltage fast activity mixed with some slow waves in the more superficial contacts (fig. 4). In needle electrodes placed more externally, such as LFT an assymetrical location of the electrodes but which also seemed to be a genuine manifestation of electrical assymetry of the frontal lobes.

*Cortical rhythms.* Plate electrodes placed in patients 2, 3, 4 and 5 recorded cortical activity from motor and premotor areas. As we already know, high voltage (about 200 $\mu$V.) fast (about 25 c/sec.) spiky activity characterized recordings from these areas. Position of the leads was checked by electrical stimulation which evoked motor responses, usually in the arms. Around the most posterior and anterior points the activity was slower.

Changes in frequency and amplitude of rhythms were occasionally observed. In patient 2 linkages 1-2 from the left plate recorded a frequency of about 10 c/sec. which sometimes increased in rate to about 18 and then returned to about 10 c/sec. The amount of change in the electrical activity was generally limited to two or three different patterns and comparison of several pages of recordings suggested identification of each linkage by its pattern. Some of the changes were specifically connected with motor activity or sensory stimulation of the patients, as explained below.

*Effect of voluntary movements and sound stimulation upon cortical activity.* In patient 3, electrical stimulation of leads 3-4 of the left plate (100 c/sec., unidirectional square waves, pulse duration 0.2 msec., 5 V., 2 mA., applied for 5 sec.) evoked a flexion of the right hand which did not disturb him. If stimulations were applied without warning while he was reading, the patient continued to read without paying attention to the movement of his hand. However, when questioned, he was aware that the hand had moved and said that the arm felt "weak and dizzy". As observed by other investigators (Penfield and Jasper 1954) recordings of electrical activity during the performance of voluntary movements showed a blocking in the corresponding cortical motor area. In figure 6 we see an example of this phenomenon. The patient was asked to flex the right hand and then to relax it in the interval between the two arrows shown in the figure. The activity was specifically blocked in linkages 2-3 and 3-4. At other times when the patient was reading and used his right hand to turn the pages a similar block of the electrical activity was observed. Movements of the legs did not produce any change in electrical activity of this cortical area.

Sound stimulation may have a more generalized effect upon the cortical electrical activity, as shown in figure 7. In patient 2, while recording from left and right plate electrodes, recorded music began at the arrow; a short moment of desynchronization appeared in the electrical activity, followed by a considerable increase of amplitude affecting most of the cortical points of both sides. The effect lasted for about 10 sec. and then slowly disappeared. Turning off the music 30 sec. later had a minor influence. Noises produced by a buzzer were able to induce a similar enhancement of the plate-recorded electrical activity in both sides of the motor and pre-

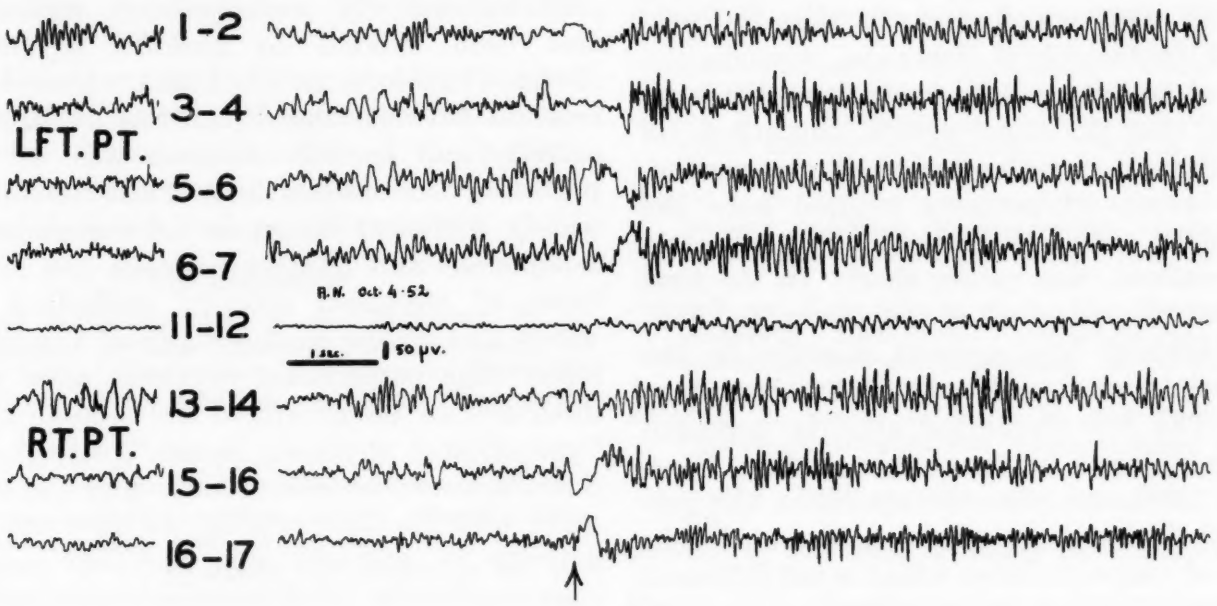



Fig. 7

Increase of electrical activity of the motor and premotor area determined by sound stimulation. At the arrow music began. Recordings taken 2 days after the operation.

motor areas. Noises such as jet planes passing over the institution could also be detected by the increase of cortical electrical activity. On the contrary, sound stimulation did not affect the electrical activity of the tip of the frontal lobes nor its depth, recorded through needle electrodes. Changes in the attention of the patients during interview did not affect the electrical activity of motor and premotor areas.

## COMMENTS

Sem-Jacobsen *et al.* (1955) indicated that a period of three days to two weeks was required after implantation for stabilization of the electrical activity in human patients. We have reported our experience elsewhere, based on extensive animal experimentation (Delgado 1955). Our conclusion was that the presence of intracerebral electrodes disturbs the electrical activity of the brain very little, or at least, that the experimental conditions do not change during the period of observation. In the group of patients studied here the observation time, determined by therapeutic considerations, was rather short. In the first hours of recording after the operation Pentothal activity was present, mainly in the superficial, but also in the most external deep leads. The fast Pentothal activity persisted in some patients for more than a day. However, a few hours after the operation the patterns of electrical activity at different depths exhibited characteristics which were different from Pentothal activity, were typical for each linkage, and were rather stable throughout the observation time. However, the possibility of lasting effects of anesthesia should be kept in mind. Penfield and Jasper (1954) in recordings taken during surgical intervention mentioned the instability of the normal electrical activity of the brain, and the modification of this activity by attentiveness, higher mental processes, voluntary movements, etc. In the motor and premotor areas we have confirmed the influence of different factors such as voluntary movements and sound stimulation upon the cerebral electrical activity. The activity of the depth of the frontal lobes, on the contrary, seemed to be rather unaffected by mental processes, motor activity, and different types of sensory stimulation.

Classifications of spikes and sharp waves have been rather arbitrary in the literature. According to Penfield and Jasper (1954) (page 588) "when a spike is prolonged beyond 60 msec., to total durations of 100, 200, or even 300 msec., it is called a sharp wave". Heath (1954, p. 164), however, describing spike activity gave a duration "from about 60 to about 200 msec." with bipolar recording amplitudes ranging from 25 to about 200 $\mu$V. Agreement with respect to labeling of spikes would be desirable, and the definition by Penfield and Jasper seems in our opinion more useful. Heath (1954) gave a special significance to the presence of spikes recorded by depth electrography and relates them to specific psychiatric diseases. Another type of electrical activity, namely, slow waves, has also been related to specific psychiatric illness (Bickford *et al.* 1953). However, a relation between these patterns of electrical activity and specific deseases was not supported by our observations. Patients with the widely different diagnoses of schizophrenia, taboparesis and anxiety neurosis had similar types of electrical activity, including slow waves and spikes, in the depth of the frontal lobes. The paroxysmal rhythmic slow waves described in paragraph 5 are similar to the "paroxysmal rhythmic bursts" described by Sem-Jacobsen *et al.* (1955), and in agreement with his observations, we have seen this activity in patients who had not received previous insulin or electroshock treatment. In our cases however, this paroxysmal activity was rather constant throughout the observation time and the pattern repeated itself with similar characteristics emerging from a background of fast activity. Changes in conversation, mood, or position of the patients did not seem to have any correlation with paroxysmal rhythmic activity.

## SUMMARY

In a group of 5 psychotic and 4 nonpsychotic patients the electrical activity of the depth of the frontal lobes was recorded for 1 to 4 days, using multilead needle electrodes. Electrical activity of the motor and premotor areas was also recorded in 4 of these patients by plate electrodes. Results were as follows:

1. Typical patterns of electrical activity repeatedly observed included: (*a*) low voltage; (*b*) alpha-like; (*c*) high voltage fast; (*d*) high voltage slow irregular; (*e*) paroxysmal rhythmic slow; (*f*) spikes and sharp waves; (*g*) other types. Some rhythms seemed to be located in determined regions of the frontal lobes.

2. Very similar spatial distribution of rhythms within the frontal lobes was found in patients with different types of illness.

3. In general the electrical activity was symmetrical in both sides of the frontal lobes. In one patient the activity was asymmetrical.

4. No correlation could be established between electrical activity of the depth of the frontal lobes, and motor movements, sensory stimulations, or changes in the mood of the patient.

5. Voluntary motor movements inhibited the electrical activity of specific cortical motor areas. Sound stimulation of the patient with music or noises increased the electrical activity of motor and premotor areas.

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# THE FORM, VOLTAGE DISTRIBUTION AND PHYSIOLOGICAL SIGNIFICANCE OF THE K-COMPLEX

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## INTRODUCTION

The K-complex of sleep and light barbiturate anaesthesia and the attenuated version of it that may be observed in some subjects in the waking state are among the most conspicuous features of the human electroencephalogram. Yet until recently the classical papers by Davis (1939) and Davis *et al.* (1939) were virtually the only sources of information about it in the literature. However, there have been some recent important papers by French workers (Gastaut 1953; Bancaud *et al.* 1953) who have studied its morphology and the psychological phenomena associated with it. Studies on special aspects of the problem have also appeared (Pampiglione 1953; Chafets and Cadilhac 1954) and a brief preliminary report of this work has been published (Roth, Shaw and Green 1953).

Davis suggested that the K-complex was analogous to the secondary discharge following sensory stimulation under barbiturate anaesthesia in cats, described by Forbes and Morison (1939). There are certain difficulties about such an interpretation which will be discussed later. Whether or not this analogy is valid, it throws little light upon the functional significance of the phenomenon in man, to whom it seems peculiar.

In this investigation an attempt has been made to throw some light on this problem by studies of the form and distribution of the phenomenon, of the influence of changing parameters of stimulation and of alterations in level of awareness and by investigations with a special technique of the changes in the electrical field on the scalp in the course of the phenomenon and in the time interval immediately preceding and following it.

## MATERIAL AND METHOD

Most of the data have been obtained from recordings carried out in 80 adult psychiatric patients for purposes of routine and specific investigations. Fifteen control subjects have also been investigated in states of normal awareness and during sleep and barbiturate anaesthesia. Many of the patients were studied in serial recordings made under barbiturate anaesthesia before, during, and after electroconvulsive treatment and before and after prefrontal leucotomy, to investigate their effects on the EEG. Only the studies before treatment will be described here. The changes in the K-complex associated with treatment will be reported in a subsequent paper. The total number of experiments exceeds 400.

Sound was the main form of stimulation used in conscious and unconscious states, but visual (stroboscopic), painful, and tactile stimuli were also employed. The auditory stimulator used consisted of an electronic switch linking the output of an audio-oscillator to a power amplifier feeding a loud-speaker. This switch caused the oscillator output to be pulsed through the loud-speaker at a controlled pulse length and pulse repetition rate. The pulse length may be varied continuously from 5 to 100 msec. and the repetition rate from once in 30 sec. to 30 times per sec. Single pulses manually controlled can also be obtained.

To induce anaesthesia a uniform procedure was followed in each experiment. A 5 per cent solution of sodium thiopentone was given intravenously at a rate of 1 cc. in 15 sec. with 5 sec. pauses between successive cc. until the patient ceased to count, after which a further cc. was administered; but a minimum dose of 4 cc. was given in each case. Previous expe-

rience had shown that this technique gave the most consistent pattern of EEG changes in serial experiments. In most cases 0.25-0.3 g. was required and the dose remained constant within narrow limits in a given patient.

## RESULTS

*K-complex in the waking state.*

The term "on effect" was given by Davis to the change originally described by her and evoked by sensory stimulation in the human subject during full awareness. Because of the site at which it shows a phase reversal French workers have used the term "vertical spike" for the phenomenon. However, apart from differences in voltage and in the relative preponderance of the various components, the overt change evoked by sensory stimuli in the EEG at different levels of consciousness is an identical phenomenon for which only the term K-complex will be used in the present paper.

In full consciousness we have been able to detect the response in 20 per cent of normals and a similar proportion of psychiatric patients; this is slightly less than the incidence of 25 per cent reported by Gastaut, while Bancaud *et al.* (1953) have found it in 50 per cent of their subjects. In the majority of our cases, however, the response was inconspicuous and only in about a third did it exceed a voltage of 25 $\mu$V. Cases in which the detailed morphology of the response can be studied in the waking state are therefore relatively rare. However, an incidence of 20 per cent in some form suggests that we deal with a physiological variation, and subjects in whom it is absent in the waking state may well have a response too small to be distinguished in the EEG. The results obtained by Larsson (1953) by means of the superimposition technique of Dawson (1947) tend to confirm this view and the presence of the response in sleep in all cases (see below) further supports it.

The first change is a surface positive wave which may be recorded over a very extensive area of the head; with unipolar leads there is a voltage peak at the vertex or near it. With bipolar recording from a series of electrodes along the mid-sagittal line there is a reversal of phase at the same point, deflections being upwards in front of it (when leads are linked to amplifier input connections in the conventional manner) and downwards behind it, indicating that the vertex initially becomes electro-positive in relation to surrounding areas (fig. 1, 2 and 3). Larsson (1953), who studied 6 cases, described the initial deflection as being electro-negative and the findings of French workers (Gastaut 1953; Bancaud *et al.* 1953) are in accord with this. But though the most prominent deflection is sometimes surface negative, careful examination has in our cases almost invariably revealed a small surface positive deflection preceding it.

The form of the response is influenced by its voltage. Most often it is seen in the conscious state as a monophasic wave of low amplitude. But where its voltage is high the response is bi- or tri-phasic in form.

Of the two other components so clearly evident in the K-complex of sleep, to be described below, the second slow wave change is occasionally seen as a brief low voltage deflection. But "spindles" are never observed in consciousness. We have found no differences in the form of the K-complex between normal subjects and psychiatric patients.

When the interval between stimuli is maintained at 3 sec. or more, responses may be evoked indefinitely in suitable subjects. With shorter intervals responses tend to become inconsistent although in a few cases regular responses have been obtained with auditory stimuli at 1 sec. When stimulation was maintained at a more rapid rate than 1 sec. (and in many cases at a longer critical interval) responses failed to appear in most cases. This result differs from that of Bancaud *et al.* (1953) who report a refractory period of about 300 msec.

Despite the phase reversal or voltage peak at or near the vertex the K-complex is extensively distributed and clearly seen in the occipital, temporal and frontal regions with bipolar or unipolar recording. We have been unable to confirm (fig. 1) that the frontal component is an artifact due to reflex facial contraction or eye closure provoked by the stimulus, as suggested by Gastaut (1953).

A brief period of suppression or diminution of the alpha rhythm is common but not invariable (fig. 1). When suppression occurs the alpha rhythm returns within a half to one sec. A startle reflex is sometimes seen but is often absent. We have not found the element of surprise stressed by Gastaut (1953) as ulation evoke responses identical in form (v.i.).

Beyond a low intensity, altering the parameters of stimulation exerts no discernible effect on the response when allowance has been made for the spontaneous fluctuation in amplitude that is characteristic of it; the K-

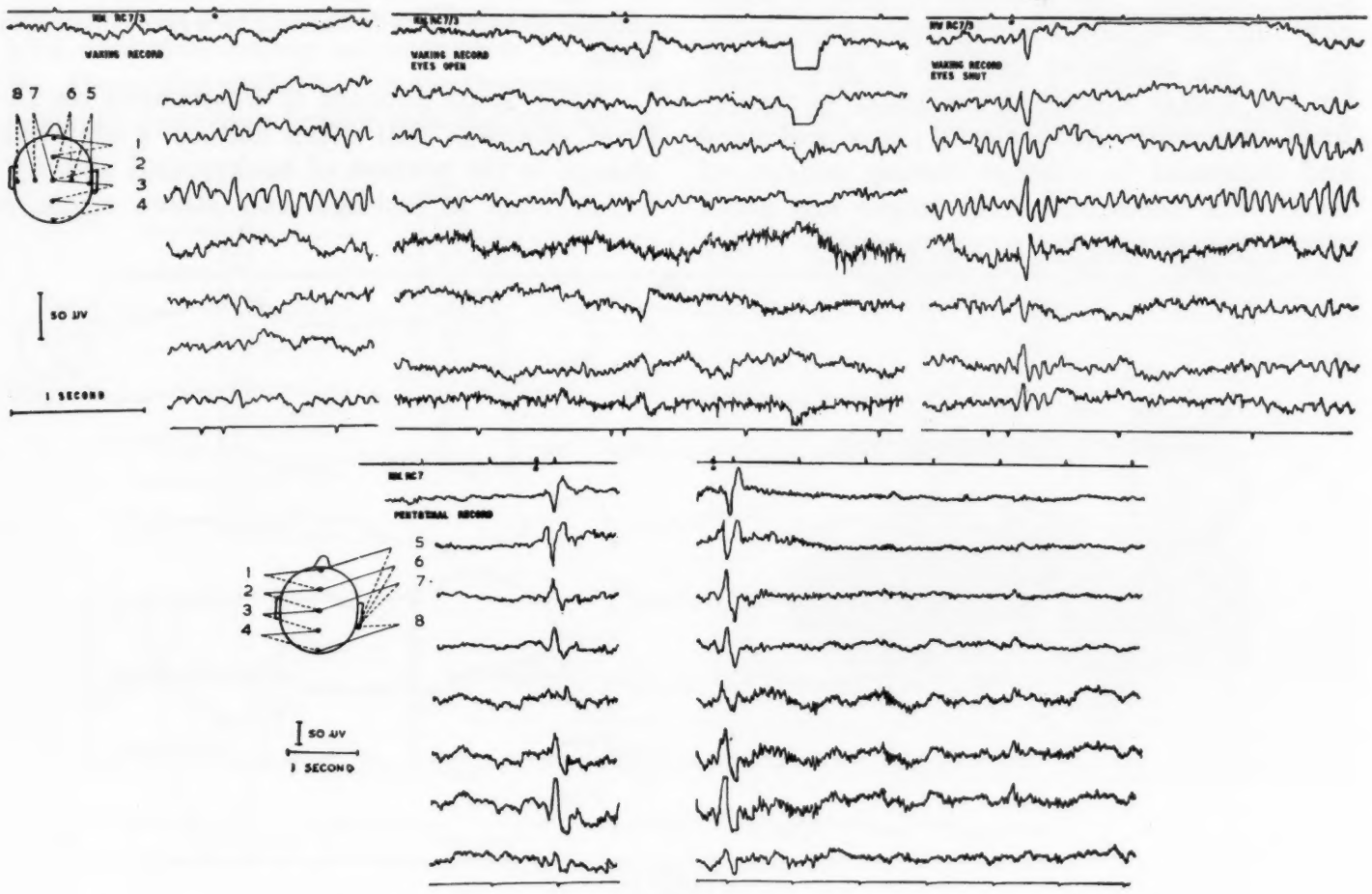



Fig. 1

The three upper responses were elicited during consciousness, the two lower ones under light barbiturate anaesthesia. The first and third upper responses were recorded with eyes shut, the middle one with the eyes open. No suppression of alpha follows the first response, while the third response is followed by a brief suppression after a short time lag. The second response can be clearly differentiated in all areas owing to the absence of alpha rhythm. The blink artefact following the response is quite distinct in form from the latter's frontal component: no facial movements were observed to accompany any of the responses. The two lower responses are more complex and higher in voltage. The slow component is ill-defined but spindles are seen particularly clearly in the monopolar leads. Note that although the main deflection in these last two responses shows negativity at the vertex in relation to surrounding areas there is a small deflection in an opposite sense preceding it seen particularly clearly in the bipolar recording Stimulus as marked by arrow on time marker trace opposite dot.

favouring the evocation of the response, to be important. Even when they have been told to expect stimuli regularly at intervals of 3-4 sec., responses could be evoked indefinitely in subjects with prominent K-complexes in full awareness. Different forms of sensory stim-

complex would thus appear to be an all or none phenomenon. But its characteristics are best studied during sleep or light anaesthesia when it is a consistent feature of the human EEG and invariably present in prominent form.

*The influence of level of awareness.*

As the patient becomes drowsy during an injection of sodium thiopentone the EEG changes to show a mixture of frequencies, with generalised fast activity, a variable amount of theta rhythm in the central regions and in the occipital areas an ill-sustained alpha rhythm. There follow stages in which rhythmic theta and then rhythmic delta activity are the dominant features of the record. On the dosage described the latter is usually brief, inconspicuous or absent; it is prolonged and increased in voltage during courses of ECT. The theta and delta stages last about anaesthesia induced by sodium thiopentone in doses below 0.6 g. (In deep unconsciousness it is of course large swinging slow waves that dominate the record.) It is after this step-like change in amplitude has occurred that the K-complex begins consistently to follow sensory stimuli, and it may be evoked only so long as this background activity does not change to one corresponding to a more vigilant state.

After some minutes of anaesthesia an intense stimulus will often induce a step-like change in the pattern of background activity, which rises in voltage and shows again a

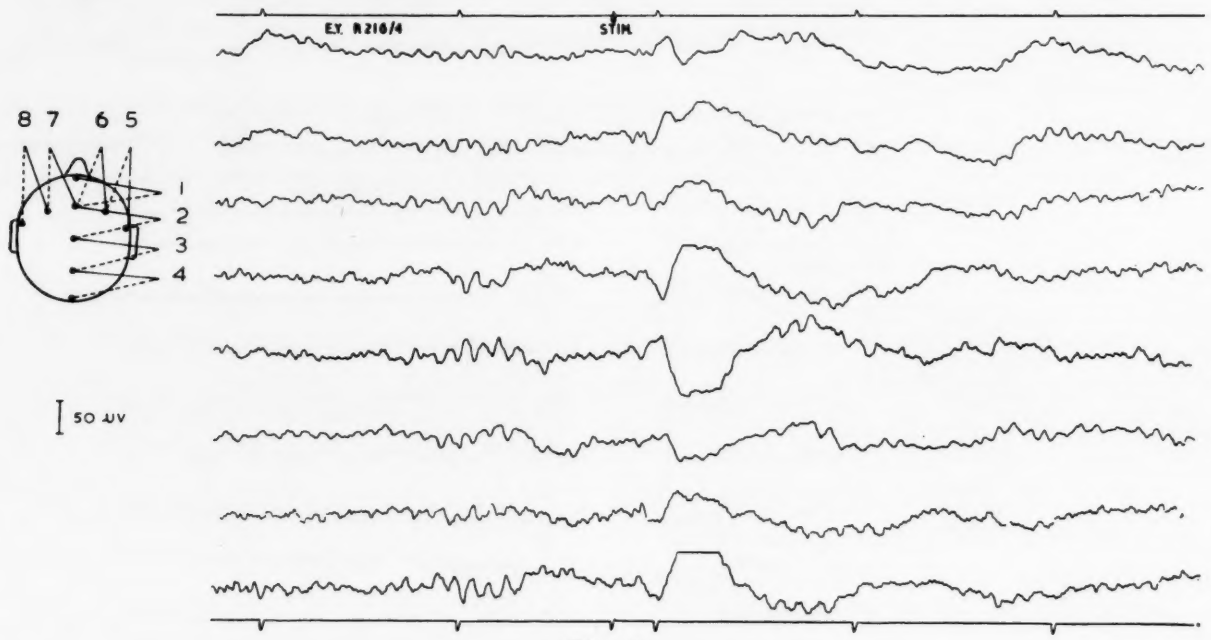



Fig. 2

The K-complex in deep sleep clearly showing all three stages of the phenomenon. The first component is short and the initial deflection indicates positivity at the vertex in relation to surrounding areas. The second component is large and at the end spindles are seen. Spindles and slow waves are also present in background activity however.

20-35 sec. but are ill-defined during the drift to normal sleep. They are succeeded by high voltage fast activity at 18-29 c/sec.; the theta, delta and beta waves all show frontal predominance in voltage. No K-complexes can be elicited during any of these phases. They occur in a most clear and consistent manner during a well-defined stage; that initiated when a sudden fall in the amplitude of beta activity has occurred. It is at this pattern of low voltage fast activity that the record tends to become stabilised both during the light sleep into which some subjects spontaneously drift under ordinary laboratory conditions and the mixture of frequencies or, less often, a prolonged stage of rhythmic waves at 14 c/sec. (see below); this change is nearly always bridged by a K-complex (fig. 5, 7 and 8). But although the new pattern may persist for 10-15 sec. no further response can be elicited until the record has resumed the more quiescent appearance of the stage of low voltage fast activity.

If the subject should become more deeply unconscious, with a corresponding change in the EEG towards a pattern of large irregular slow waves with spindles, the K-complex appears less consistently and is less clearly de-

marcated from background activity. With deeper unconsciousness it is no longer elicitable.

During sleep and anaesthesia three relatively distinct components may be differentiated in the K-complex (fig. 1, 2 and 5); (i) the first and most consistent is a sharp wave lasting ⅕ to ⅓ of a sec. This resembles the only distinguishable component of the K-complex elicitable during consciousness; in sleep too, the initial deflection is electro-positive in unipolar recording from a mid-sagittal line of electrodes. But the sharp wave is now more complex in form, being bi- or tri-phasic and occasionally re-duplicated; it is interesting also that its duration is approximately twice that of the sharp wave response during consciousness where this is elicitable. The voltage peak and phase reversal are localised at the same electrode on the scalp as in consciousness. (ii) The second stage, rarely discernible in the conscious state, is a much slower wave in which the sign of the main deflection of the first component is reversed in unipolar recording. Its voltage distribution differs from that of the first component in that it shows a peak or plateau in the anterior part of the head rather than at the vertex. It varies in amplitude and it is augmented during a course of ECT, as also following prefrontal leucotomy (Roth, Shaw and Green 1955). (iii) A generalised burst of 12-14 c/sec. activity follows. This is easily mistaken for alpha rhythm on account of its quasi-sinusoidal form and because when full arousal occurs it is followed by a mixture of frequencies among which the alpha rhythm is distinguishable. But the spindle phase of the K-complex has a mid-frontal voltage peak and a corresponding phase reversal in bipolar recordings. We have never seen true alpha rhythm following immediately upon a spike or slow component of the K-complex in states of unconsciousness.

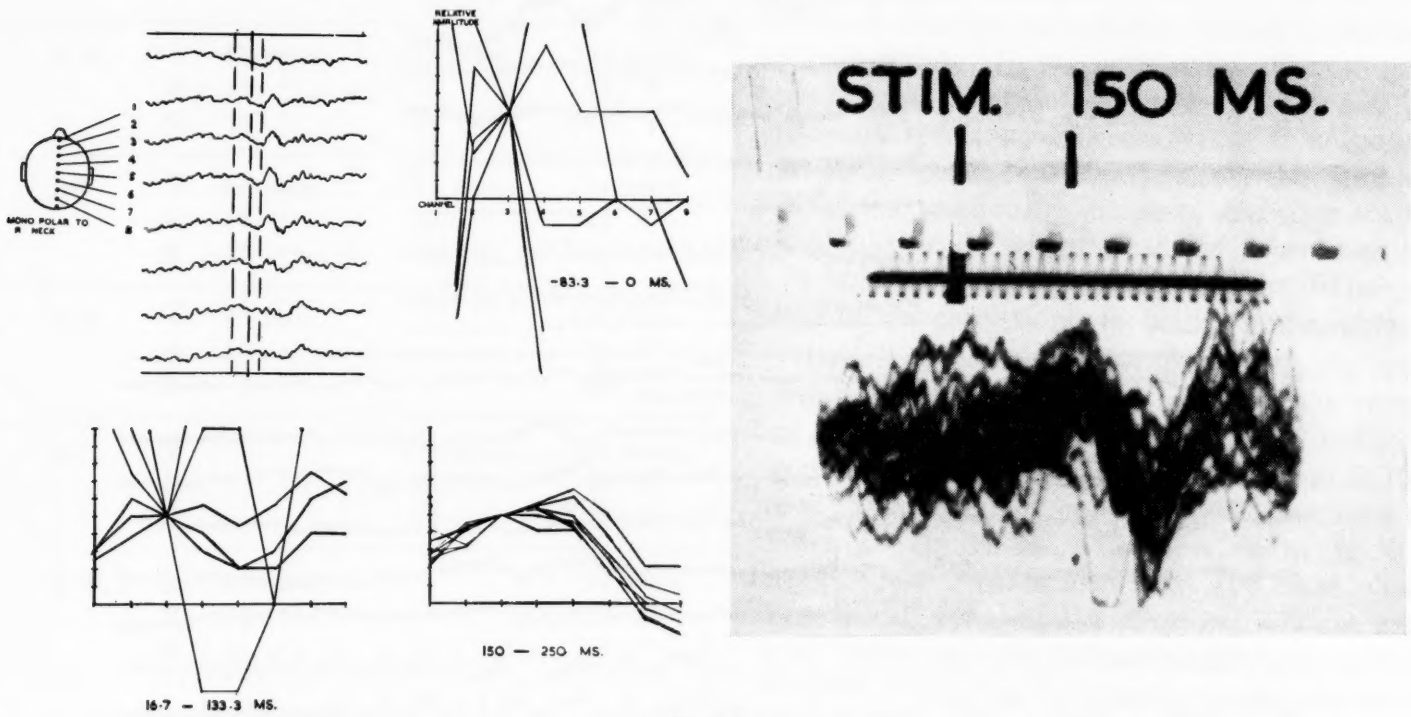



Fig. 3

The measurement of latency of the K-complex by photographic superimposition method and by voltage distribution analysis. Photographic superimposition of 25 K-complexes shows the first event to occur at 150 msec. Three groups of successive "normalised" voltage distributions are also shown. Only the last group are congruent and the first of these distributions occurs at 150 msec.

The relative size of the three components is variable. The slow wave is usually less conspicuous than the first component in light sleep although in some individuals it is consistently large in amplitude and encroaches on the sharp wave. At a deeper level of sleep however, the second component is nearly al-

ways of high amplitude and prolonged and the sharp wave component seems often to be cut short, attenuated, or even absent.

A voltage peak at some point in the midline is thus always demonstrable for the first and third components of the K-complex and occasionally for the second. This often causes their generalised distribution, which is a consistent feature that makes the K-complex unique among responses to sensory stimulation in subjects, but elicitable in everyone in states of unconsciousness (Roth and Green 1953). The two phenomena seem in fact to be evoked or suppressed under similar conditions suggesting some relationship between them. They both appear in and are confined to the same stage of sleep and light barbiturate anaesthesia: that initiated when the EEG becomes stabilised in a pattern of low voltage fast activity. K-complexes are often followed by

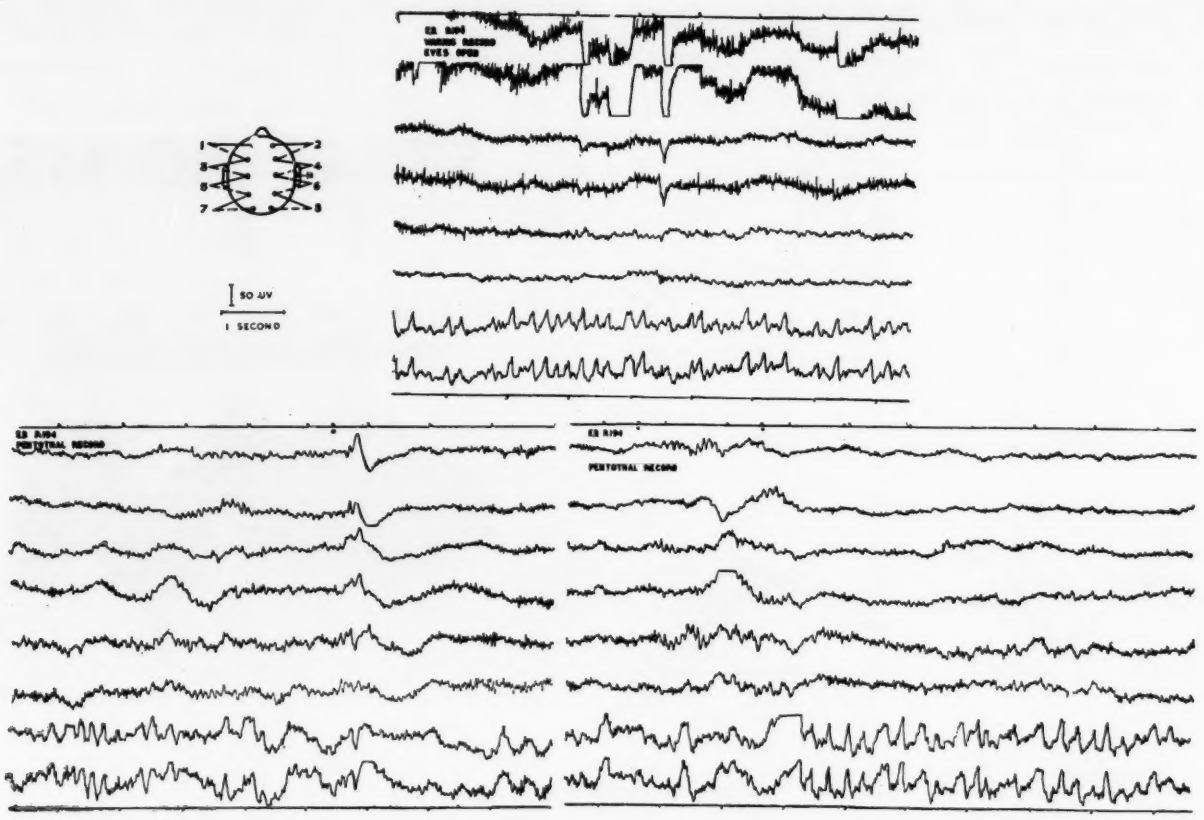



Fig. 4

The upper trace shows occipital lambda waves in the waking state with much eye artefact in the frontal leads. Of the two K-complexes during Pentothal anaesthesia shown in the lower trace that on the left has a clearly defined first component which in the occipital region resembles in form the preceding lambda waves while the second has no first component other than an occipital sharp lambda-like wave; the slow component is followed by a burst of lambda waves.

man, to be overlooked; this problem is discussed later.

The fact that the K-complex is universally present in states of light anaesthesia and sleep suggests that its absence in the waking state in the majority of subjects may well be due to its low voltage, its masking by background activity, or both. In this respect it resembles the lambda wave (Evans 1953), another recently described EEG phenomenon present in clearly defined form only in a minority of an irregular discharge of occipital lambda waves, which closely resemble the occipital component of the complex (fig. 4). If anaesthesia is pushed to very deep levels both the K-complex and lambda waves disappear. Finally, as in the case of the first component of the K-complex, the mean duration of the lambda wave is approximately doubled during sleep.

The latency of the response is difficult to determine in the original EEG since the onset

of the phenomenon is usually not sufficiently clearly demarcated from background activity. Measurements made in 5 cases in which there were relatively clearly defined responses during consciousness and/or natural sleep as well as during light barbiturate anaesthesia are shown in table I. The latency has been

TABLE I

Latency of the K-complex in five subjects during consciousness, natural sleep and Pentothal sleep.

| *Subject* | | *Waking* | *Natural Sleep* | *Pentothal Sleep* |
|---|---|---|---|---|
| A.Y. | $\bar{x}$ | 85 msec. | 170 msec. | 168 msec. |
| | S | 15 " | 74 " | 74 " |
| | N | 15 " | 27 " | 41 " |
| BC | $\bar{x}$ | 55 msec. | 106 msec. | 114 msec. |
| | S | 16 " | 22 " | 29 " |
| | N | 13 " | 11 " | 59 " |
| C.B. | $\bar{x}$ | 43 msec. | | 126 msec. |
| | S | 10 " | | 19 " |
| | N | 8 " | | 92 " |
| D.C. | $\bar{x}$ | | 103 msec. | 120 msec. |
| | S | | 16 " | 26 " |
| | N | | 20 " | 20 " |
| E.W. | $\bar{x}$ | 80 msec. | | 97 msec. |
| | S | 36 " | | 26 " |
| | N | 84 " | | 52 " |

$\bar{x}$ = mean latency.
S = standard deviation of the mean.
N = number of responses.

determined during Pentothal sleep in a large number of other cases but these were the only ones in which an adequate number of clearly defined responses at different levels of awareness were present. A number of points emerge. There is a considerable range of variation of latency during consciousness as well as sleep and barbiturate anaesthesia; the range of variation in normal subjects and psychiatric patients evidently merits a fuller investigation. There is also a considerable scatter of the values as shown by the standard deviations in each of the 5 subjects, greater in some than others. The large scatter is probably due, to some extent, to the error involved in measurement, since latencies to the first peak of the sharp wave component (determination of which involves less ambiguity) have shown in a number of cases smaller standard deviations. The mean latencies during sleep and light barbiturate anaesthesia are almost identical but it will be noted that in 2 of the cases latency during consciousness is almost exactly half, and in one case very close to one-third of that measured during sleep and anaesthesia. In the fourth case no such simple relationship exists.

Brazier (1953) has previously drawn attention to the increase in latency of the response to sensory stimulation during anaesthesia in animals. But a suggestion of a simple quantitative relationship between latencies at different levels of awareness for a response that is a consistent feature of the human EEG is of particular interest. A fuller study of latency at different levels of awareness in a sample of normal subjects and in different psychiatric conditions is being undertaken.

Some observations during anaesthesia with Dawson's superimposition method in a number of cases reveal the first clearly defined event in the response at between 50 and 160 msec. The result of one set of observations is shown in figure 3. The first event in the superimposed traces occurs at 150 msec. The normalised voltage distributions (Shaw and Roth 1955a) are also shown and it is seen that the first of a group of congruent distributions during the sharp-wave component of the K-complex (the only one definable in this instance) also occurs at 150 msec. after the stimulus. This tends to confirm that the first of this group of congruent distributions may be used to define the latency of the K-complex (Shaw and Roth 1955a).

When identical auditory or visual stimuli were given at regular intervals of more than 3 sec. responses appeared for each stimulus. With more frequent stimuli responses were usually irregular and ill-defined, while with stimuli at 1 in 2 sec. or less all responses were usually suppressed after the first 2-3 stimuli. There was some variation in this respect however, the K-complexes commencing to decline in amplitude when the interval between stimuli was 5 sec. in some subjects, while in one individual responses were elicited with 1/sec.

stimuli for periods of 15-20 sec. But these cases were exceptional and stimuli so frequent usually caused complete suppression (fig. 5). This effect of rapid stimulation was identical with that observed with continuous sounds, which after an initial response or two did not evoke any K-complexes for prolonged periods of stimulation.

Adaptation, as described by Pampiglione (1953) and Chafetz and Cadilhac (1954), thus occurs only in association with continual stimulation or with discreet stimuli that are very close together. This is clearly shown in figure 6, which gives a complete record of all stimuli and responses during an experiment. At the beginning of the chart, which corresponds to a stage of low voltage fast activity, no responses are elicited. The first evoked response follows the 16th stimulus. Thereafter responses occur regularly apart from occasional ''misses'' that tend to occur at random. There is nothing to suggest adaptation in this case until the stimuli are given at intervals of 2 sec. When the interval is lengthened again fairly regular responses recommence. Apart from the few pinpricks shown stimulation was utilised throughout the experiment. With stimuli at intervals longer than 3 sec. we have observed no tendency to adaptation either in sleep or in the waking state. It is of interest that during ''adaptation'' to continuous or frequent stimuli the system responsible for the K-complex is not refractory to stimulation. During continual stimulation with sound, K-complexes may be elicited by intermittent auditory, visual or other stimuli in the normal way (fig. 7) and this also holds for auditory stimuli introduced at random during a sequence of such stimuli given at regular 1/sec. intervals that is not itself evoking responses. Adaptation would thus appear to be determined by the timing and not the quality of

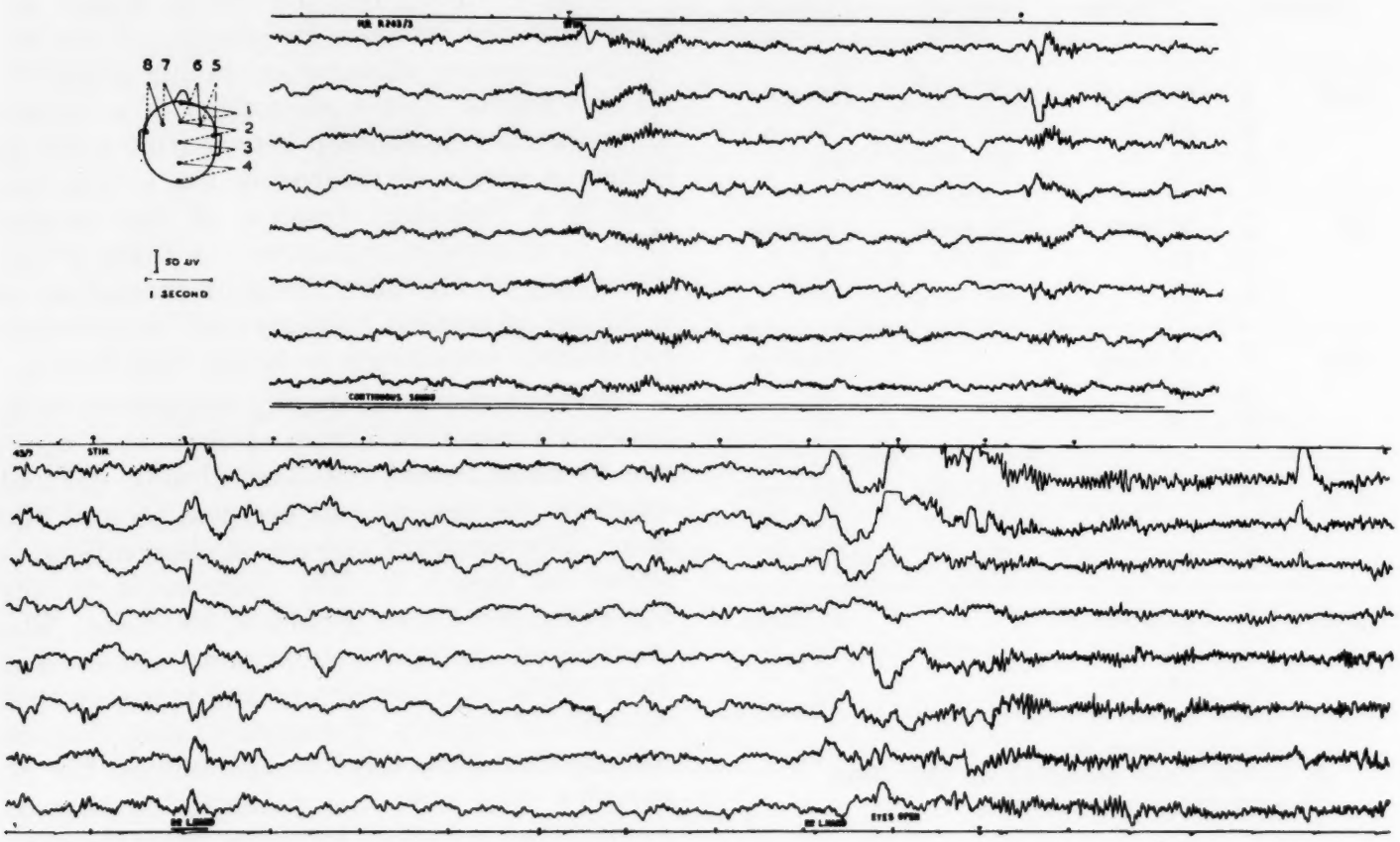



Fig. 5

K-complex elicited by stimuli superimposed upon continual and frequent interrupted stimuli. In the upper traces the continuous sound elicits no responses while two brief clicks during continual stimulation each elicit K-complexes. In a lower tracing clicks at 1/sec. intervals evoke no responses, whereas two pinpricks given during the series of clicks evoke K-complexes, the second leading to full arousal.

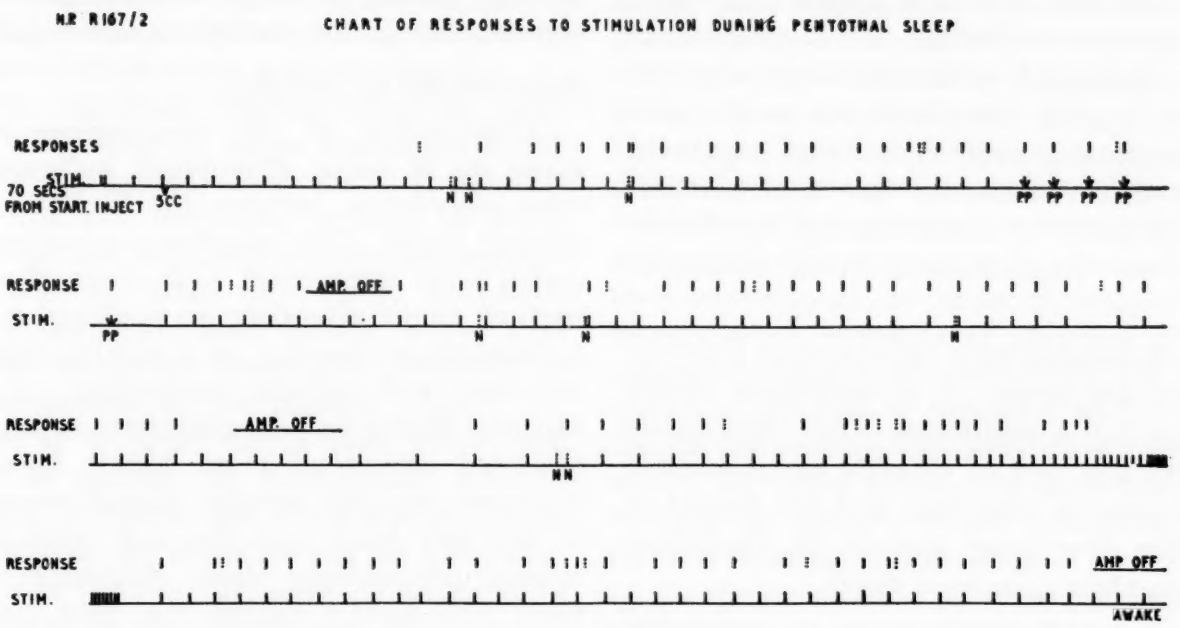



Fig. 6 — 10 sec.

In this record of a complete experiment every stimulus given and each spontaneous and evoked response recorded is shown. Most intervals between stimuli greater than 5 sec. N = noise, : = spontaneous responses.

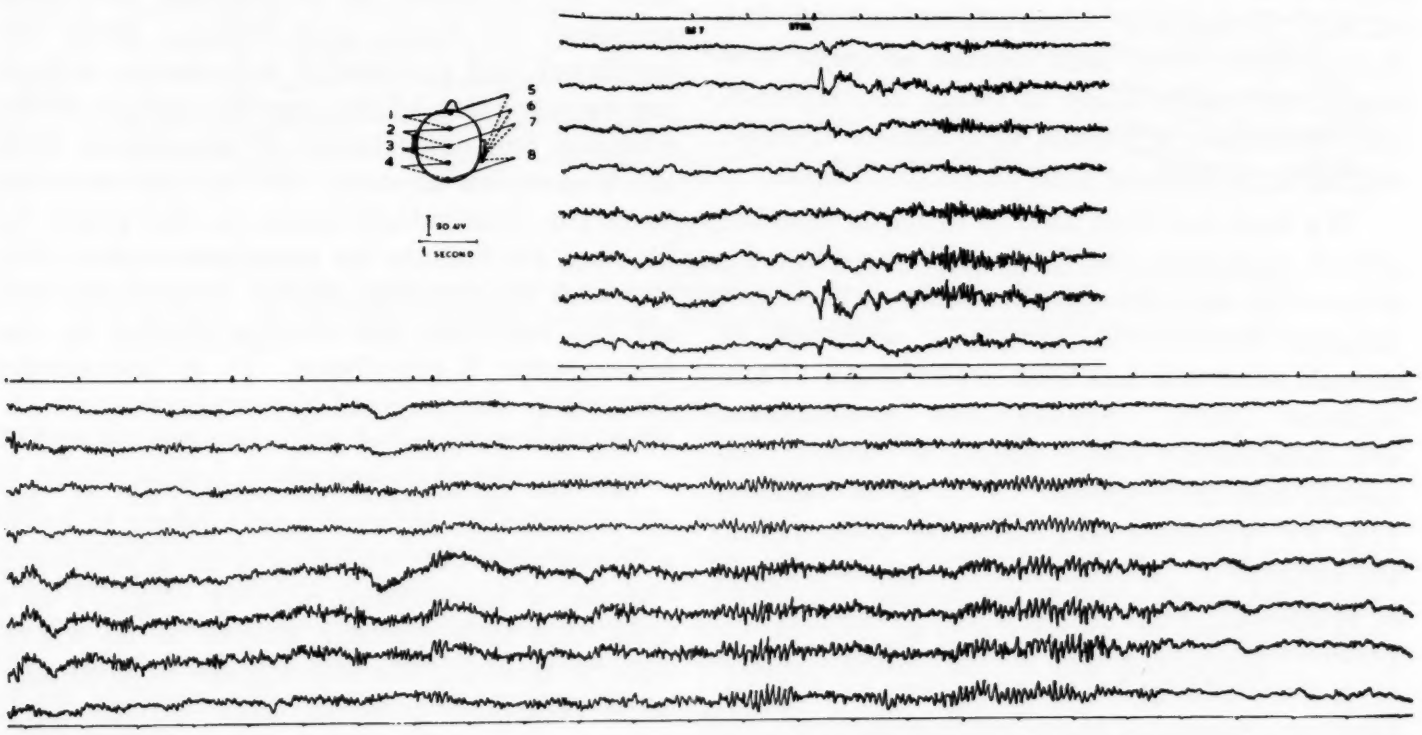



Fig. 7

Sudden change in pattern of background activity commencing with K-complex initiated by auditory stimulation. The stimulus evokes a K-complex which is followed by a sharp rise in voltage of the EEG with synchronised 14 c/sec. spindle activity from all areas. That this change in pattern is a stage in the development of arousal is shown by the fact that it is sustained by repeated stimulation and results after the last stimulus but one in an alpha dominant record. When stimulation is discontinued, this subsides to be followed by the very low voltage irregular fast activity which had preceded the stimulus. Stimuli shown by thick black strokes in upper line trace.

successive stimuli. And a suggestion emerges, that the system mediating the K-complex is specially concerned with transient signals; this would explain its quiescence in the presence of sustained, or frequent and regularly recurring disturbances in the environment. For at this level of consciousness the latter may not be discriminated from continual stimuli.

There is considerable spontaneous fluctuation in the amplitude of K-complexes under light Pentothal anaesthesia. Our impression agrees with the view of Chafetz and Cadilhac that K-complexes vary less and the record is more stable over long periods in Pentothal anaesthesia than in normal sleep.

In sleep and anaesthesia as in consciousness, altering the parameters of stimulation (other than time interval between stimuli) exerts no effect upon the regularity or form of the responses. But after some minutes have elapsed, on the dosage of barbiturate described and throughout experiments carried out during light sleep, loud intense or quite new stimuli are more likely to evoke K-complexes that culminate in partial or complete arousal, and such complexes tend to be prolonged.

We have not been able to confirm that the system mediating the K-complex may be conditioned to respond spontaneously at the fixed interval maintained during a sequence of stimuli after this has been interrupted (Pampiglione 1952). Spontaneous K-complexes will occasionally occur during a "silent" interval, but they appear to do so at random (fig. 6); vigilance will moreover often reveal the cause of a "spontaneous" response, which is commonly some unobserved stimulus; the periodic click of a half-minute impulse clock or a particularly loud expiration by the patient are examples from our experience.

As in consciousness, so in sleep and anaesthesia the form of the K-complex is identical for auditory, visual, tactile, and painful stimuli. Bancaud *et al.* (1953) have described differences in latency for the different modalities of stimulation. Since the scatter for latency values is large this interesting observation calls for statistical investigation.

*Relationship to Arousal.*

Observation of the unconscious subject while he is being stimulated indicates that some association between the K-complex and arousal exists. The responses are often associated with some overt indication of arousal such as slight alteration in position, a grunt, a cessation of snoring, or a sudden change to less deep and regular respiration. A simultaneous change in skin resistance is sometimes observed (Bancaud *et al.* 1953). In one experiment regular painful stimuli were given to the left hand and the link with arousal seemed particularly clear. Although the patient was lightly asleep the first pin-prick (after 10 min. anaesthesia) produced a jerking movement of the hand which was simultaneous with the K-complex. Thereafter each pin-prick that evoked a K-complex was followed by a jerk of the hand; but some pin-pricks were not followed by a complex and they provoked no hand jerk either. More coordinated and purposeful movements reflecting appreciation of the specific nature of the stimulus are not elicited in association with the K-complex as such. We are not satisfied from the illustrations given in the paper by Davis *et al.* that, in the experiments they cite, in which the sleeping patient himself switches off the stimulus, the changes evoked by the latter were K-complexes. It is noteworthy that when unequivocal K-complexes were elicitable no purposeful response was evoked.

As the effects of barbiturate begin to wear off stimulation is increasingly prone to evoke a K-complex that culminates in a prolonged change of background activity (fig. 5) of a kind that subsequently proves to be a prelude to arousal; the third stage is prolonged to a sustained burst of high voltage 12-14 c/sec. activity with an admixture of 4-7 c/sec. waves in the central regions and low voltage fast activity at 20-28 c/sec. in the frontal area. It is this pattern of mixed frequencies with a dominant 12-14 c/sec. component that immediately precedes the alpha dominant EEG (fig. 7) which accompanies the patient's

final arousal. But the first indication of awakening occasionally occurs earlier during the burst of 12-14 c/sec. activity (fig. 5).

Before this final response there has often been a succession of large K-complexes followed by a relatively long stage of spindles and/or a mixed frequency pattern in which the process that culminates in arousal appears to have been cut short (fig. 5, 8). A spindle or mixed frequency stage lasting longer than 10-12 sec. is almost invariably followed by complete arousal of the patient (fig. 7, 8). Moreover it is often found that when such changes in pattern of background activity first begin to follow the K-complexes during an experiment the situation can be controlled at will, for further intensive stimulation in the stage of mixed frequencies will usually awaken the patient (fig. 5, 8). But if stimuli are withheld and disturbances in the environment can be avoided the EEG will return to the quiescent stage of low voltage fast activity (fig. 5) when further K-complexes may be elicited. The situation is now unstable, however, and a stimulus will sooner or later be certain to evoke a K-complex that culminates in full arousal.

Not only is the form of the few responses preceding the final arousal very similar to that of the last K-complex (as in figure 8) but during them the subject may change position, mutter and seem about to awaken when movements subside and he succumbs again to sleep. This may also be observed with K-complexes of typical form, i.e. with an abbreviated third stage. All such pre-arousal responses differ from the final one (fig. 8) only in that the "spindle" stage seems to be prematurely terminated by the reappearance of low voltage fast activity; correspondingly the arousal process appears to be reversed. If this interpretation of the usual K-complex as the physiological correlate of abortive arousal is correct its failure to culminate in the changes shown at the end of figures 5 and 8 must be due to the coming into play of some compensatory influence which cuts short the process, restores the pattern of low voltage fast activity and thus maintains sleep.

In the production of these changes we are evidently observing the influence of some system concerned with regulation of the level of consciousness and the correlated pattern of cerebral electrical activity. It is pertinent to ask therefore whether they are mediated by the diffuse projection system. Some light has been thrown on this problem by studies of the voltage distribution of the K-complex.

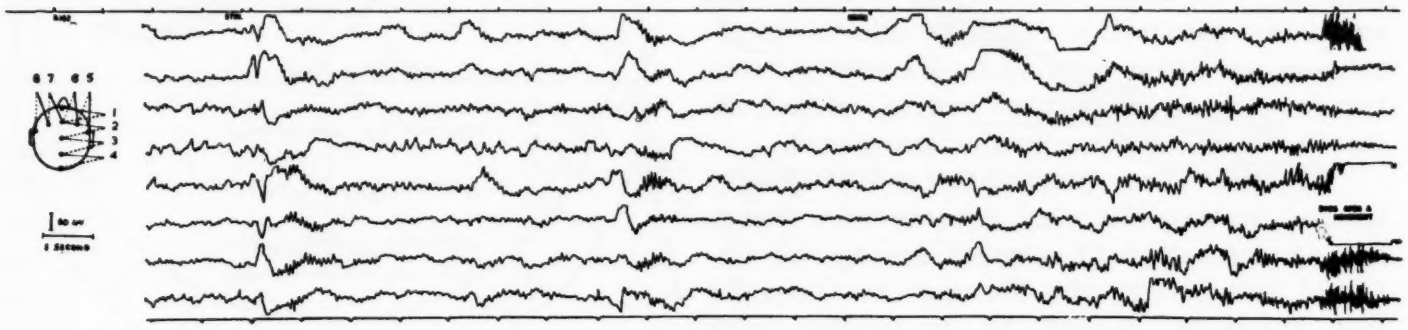


Fig. 8

Three K-complexes are shown. The last is followed by a prolonged burst of synchronised 12-14 c/sec. activity (with an admixture of faster and slower rhythms) and culminates in full arousal. In the two preceding responses the spindle stage is consistently cut short and arousal aborted.

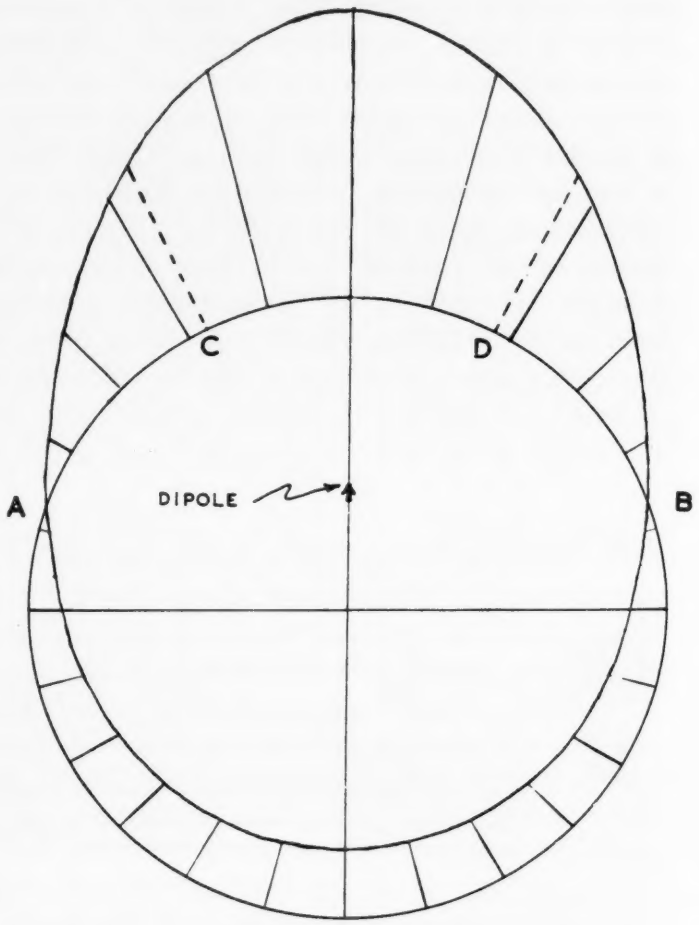
*Voltage Distribution Studies.*

Although French workers (Gastaut 1953) were unable to obtain corticographic evidence for the hypothesis that the K-complex corresponds to a discharge of the cingulate gyrus their view is supported by the consistent finding of a phase reversal in two planes of space

at or near the vertex. However, although some degree of diffusion of a focal change at the cortex would occur owing to the intervention of the brain's overlying coverings a distribution as extensive as that found on the scalp in the case of the K-complex particularly during sleep cannot be so explained. But, a process of sequential transcortical excitation spreading from a primary site at the vertex to more peripheral areas could explain the extensive distribution of the electrical change. A second possibility would be propagation as a result of extrasynaptic stimulation, the spread occurring in a manner independent of neuronal connections. A third possibility would be cortical spread resulting from interaction between the primary site of cortical discharge and some subcortical nucleus such as the thalamus with which it has intimate feedback connections. Lastly, the extensive distribution could be due to simultaneous excitation of widespread areas of cortex from some subcortical centre, as for example, via the diffuse projection system.

The first three possibilities would clearly involve moving electrical sources or a changing configuration of sources during the interval occupied by the K-complex. Only the last possibility would be compatible with evidence indicating that the electrical source or sources responsible are stationary during the interval occupied by one or more components of the K-complex. A preliminary approach has been made to the solution of the problem by means of the technique of "potential distribution analysis" (Shaw and Roth 1955).

Now when the voltage distribution of the K-complex over the head as derived in unipolar recording from a line of electrodes in the mid-sagittal plane, is measured at intervals of 1/60 sec., the results "normalised" and the sequence of distributions plotted, a marked degree of consistency in the shape of the curves is observed. The result for the first part of the K-complex is a succession of congruent curves which are roughly bell-shaped (fig. 10). The shape is similar to that derived by Brazier, although the consistency she assumed for the whole K-complex is not in fact obtained until the curves are normalised and then only for its first part. When a similar procedure is carried out in the case of bipolar




VOLTAGE DISTRIBUTION ON SURFACE OF SPHERICALLY BOUNDED MEDIUM

Fig. 9

The figure shows the voltage distribution on the surface of a spherically bounded homogeneously conducting medium containing a dipole source, the medium outside the boundary having zero conductivity. The curve is drawn using polar co-ordinates with the centre of the sphere as origin, but the surface of the sphere corresponding to zero potential. Radial ordinates outwards from the sphere surface are therefore positive and ordinates inwards from this surface are negative. The distribution is shown for a plane containing a dipole whose axis lies on a diameter in this plane, the dipole being 0.6 R from the surface. In calculating this distribution; $\frac{M}{R^2}$ was taken as equal to 1 where M = dipole moment; R = radius of sphere. (The potential is proportional to $\frac{M}{R^2}$)

recording which measures the relative gradient distribution or gives the first derivative of the voltage distribution curve a series of congruent S-shaped curves is obtained (fig. 11). This agrees with what would be expected from the shape of the voltage distribution curve since a roughly bell-shaped curve has two gradient maxima of opposite sign, one on each arm, while the gradient value at the summit which lies between them is zero. During the second component of the K-complex the tributions lack congruity (Shaw and Roth 1955).[1]

Further investigation including cortical and depth recordings are evidently indicated, particularly as the questions raised are of some general importance. But this source of evidence favours simultaneous activation of widespread areas of cortex as the most likely of the four possible explanations for the extensive distribution of the K-complex; and this suggests that some diffuse system of pro-

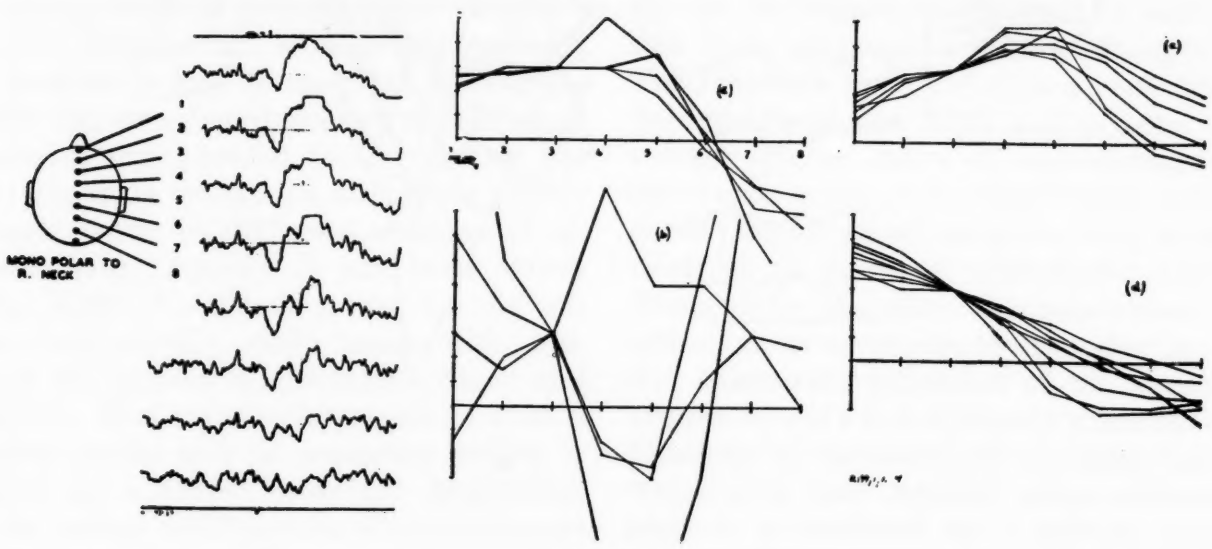



Fig. 10

In (a) is shown four normalised distributions for the time instant from the commencement of the stimulus to 67 msec. later and constitutes an analysis of the spontaneous activity occurring at the time of the stimulus. (b) represents the interval 83-133 msec. after the start of the stimulus. (c) represents the interval 150-233 msec. which covers the duration of the first component of the K-complex. (d) shows the corresponding normalised distributions for the interval 250-383 msec., during the second component of the phenomenon. The scale on the abscissa expresses relative amplitudes. The numbers on the ordinate indicate the channels. See also examples of potential distribution analysis in K-complex under Roth and Shaw (1955 a). (The ordinate lines drawn for the measurement of the voltage distributions have failed to emerge in the photographs of the EEG in this figure and in figure 11.)

distributions are again congruent but different in shape from that observed in the case of the first. These congruent patterns cannot be derived from any part of the EEG record but are relatively specific. Thus there are marked dissimilarities in the shape of the curves within the group of distributions immediately preceding the K-complex. It has also been shown in relation to other phenomena, as for example the slow wave activity evoked by barbiturate during a course of ECT that the dis-

jection is involved. But since the distributions for the two components are different, they presumably result from activation of distinct populations of cells. It has not been possible to study the third component so far,

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1 It is appreciated that "congruity" needs to be defined mathematically and methods for doing this are at present under examination. Meanwhile, qualitative descriptions are justified for distinguishing between such extreme differences in degree of congruity as are obvious to visual inspection.

since for waves at this frequency more precise recording methods would be required for potential distribution analysis.

How the reversal of phase in two planes in the midline, which is always present at the vertex in the case of the first components, and is sometimes seen in a more anterior position for the second, are to be interpreted is not at present clear. But in the case of another phenomenon, for which diffuse activation of cortex has been postulated, namely the spike and wave complex, a mid-frontal phase reversal is quite commonly observed (Jasper and Fortuyn 1947). One possible explanation for such phenomena is that the cells concerned, though diffusely distributed, have maximal concentration near the site of phase reversal. More direct cortical and sub-cortical records

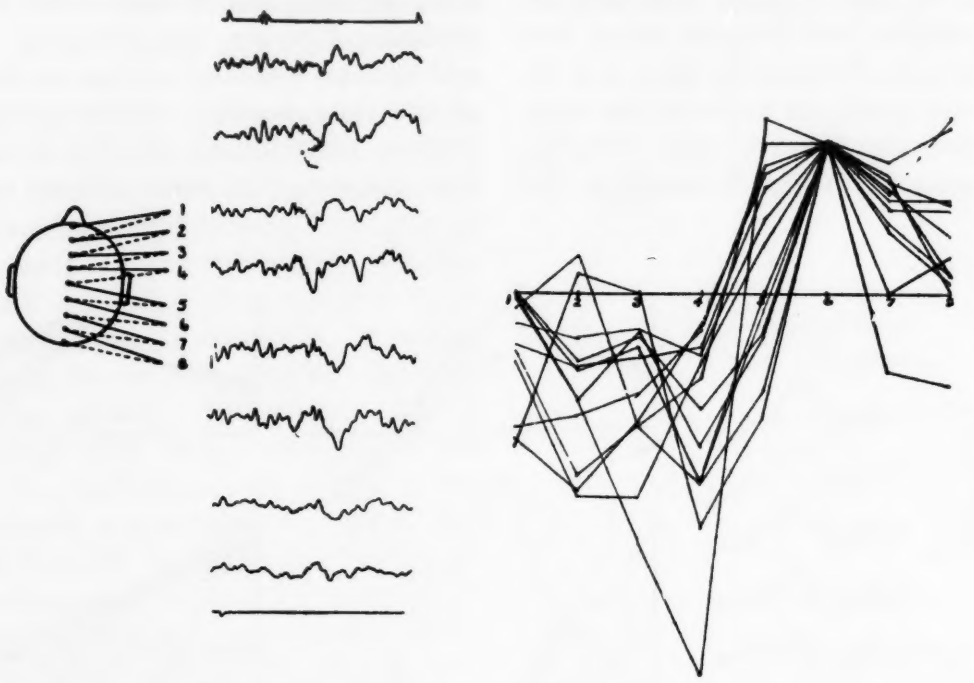

Fig. 11

The EEG record shows a K-complex recorded by the bipolar method, and the figure to the right of it the gradient distribution during its first component. The distributions are roughly S-shaped and congruent during this interval. 12 distributions at 1/60 sec. intervals from 0.2 sec. after beginning of stimulus. (1000 c/sec. × 5 msec.). The lower left figure shows the mean distributions for the first component of three responses with, on the right, the means for the same component when a few very eccentric distributions have been excluded.

ought to throw further light on this problem too.

Brazier's view that the distribution she derived for the K-complex was consistent with the presence of a dipole whose axis was perpendicular to the surface was derived from a study of the distribution at the surface of a finite spherical conductor. We have used a different formula (Shaw and Roth 1955) to plot this distribution in polar diagrams and it is seen (fig. 9) that the voltage becomes negative at a point on the surface dependent on the position of the dipole.[1] This reversal of sign in the distribution is not shown in Brazier's figure but is important since *at this point a phase reversal is seen in unipolar recordings.* Moreover the two distributions for dipoles at right angles and parallel to the surface are not two separate situations but parts of one continuous curve in different sections of an electrical field. Finally it has been shown that the depth of a dipole source can be calculated from certain easily measurable constants of the surface distribution (Shaw and Roth 1955). But many refinements of such a theoretical model will be necessary before it can serve as a useful basis for hypotheses about the nature and location of physiological sources.

## DISCUSSION

Davis (1939 a and b)who was the first to study the K-complex, and a number of other workers (Gastaut 1953; Bancaud *et al.* 1953) have regarded it as analogous in part or as a whole to the secondary discharge (Forbes and Morison 1939). However, in view of its heterogeneity, the tendency to rhythmic recurrence of the second and third components, the phase reversal in the mid-line always shown by the first two components, and its disappearance under barbiturate anaesthesia (which augments the secondary discharge) the analogy has little objective foundation. The repetitive after-discharges that follow the primary spike at specific afferent areas (Bartley and Bishop 1933; Adrian 1941; Bremer 1943, 1949; Chang 1950) show some resemblance to the K-complex in being compressed or abolished by deep barbiturate anaesthesia. But though more extensive than the primary spike they do not extend far beyond specific afferent areas nor have they the heterogenous form of the K-complex. The K-complex cannot in other words be the after-discharge following upon specific primary responses.

Any theory as to the psychophysiological significance of the K-complex must account for all the known facts about it and should link them if possible in a meaningful way. The facts are that: (i) it is a consistent feature of the human EEG and present at high voltage during states of unconsciousness; in the awake state it is identifiable only in a small proportion of subjects; (ii) it is identical for all forms of stimulation and uninfluenced by changing the parameters of the latter. In other words, the complex is a crude and inaccurate reflection of the stimuli that evoked it; (iii) it is diffusely distributed particularly in the states of unconsciousness for which it is most typical: some evidence suggests it is mediated by a diffuse projection system to the cortex; (iv) it has 3 distinct components and the earliest detectable change is a surface positive one; (v) it bears some relationship to the process of arousal.

This last fact is probably the most crucial and significant one, for it suggests the lines along which a unifying theory may be constructed. It is true, as Walter (1953) has pointed out that the K-complex in its typical form, with its abruptly terminating spindle stage, is associated with effective maintenance of sleep rather than arousal. A process inimical to arousal must in fact come into operation at some stage after the stimulus when the K-complex is of this form. But since complexes differing only in the longer duration of the stage of 12-14 c/sec. activity are associated with full awakening (fig. 8), this presumably occurs after the third stage has begun. It is difficult therefore to regard any part of the K-complex as the correlate of a sleep-protecting mechanism.

[1] In the case of a surface within an infinite medium this point is marked by the intersection of the surface with the perpendicular bisector of the dipole; for the finite medium the relationship between this point and the dipole position is more complex.

It is clear that the subject from whom the K-complex is elicited gleans some crude information about the disturbance in the environment that evoked it. This is shown by the fact that some subjects manifest with many or all K-complexes elicited a response such as a movement, change of position, an alteration of respiratory rhythm, or change in skin resistance; this may be vaguely purposive as in the change in position of a pricked hand. The vague memory some patients have after arousal, of a recurring disturbance while they were asleep, confirms this; the qualitative features of the stimulus are not identified unless stimulation has been continued into the stage of high voltage 12-14 c/sec. activity or beyond it into the alpha dominant stage when the K-complex can no longer be elicited. It would seem that so long as an EEG pattern characteristic of sleep prevails the brain can register within limits the occurrence of a transient disturbance but is incapable of further specification. These observations sanction only the inference that the K-complex is a physiological correlate of a crude perceptual process, one which may be appropriate to a primitive state of vigilance. However, that this crude perception *tends to* initiate arousal is suggested by the fact that not only are there typical K-complexes with abbreviated spindle stage and no arousal on the one hand (fig. 2 and 5), and K-complexes with a prolonged high voltage stage at 12-14 c/sec. and full arousal on the other (fig. 8), but also K-complexes with "spindle" stages of intermediate duration and unequivocal partial arousal in between (fig. 7). It is therefore in accordance with the facts to regard K-complex tentatively as the physiological correlate of both a crude perception and an abortive arousal.

If it is correct to attribute such a psychological role to the K-complex all the other known facts (v.s.) can be accounted for in a simple and parsimonious manner. That it should be a consistent and prominent feature of the human EEG only in states of unconsciousness is what one would expect of a phenomenon associated with the transmission of crude undifferentiated information. Its relative infrequency, smaller amplitude and somewhat less diffuse distribution in full awareness suggests that it may then have little or no functional significance. This is by no means a unique example of a response elicitable at but probably irrelevant to a certain level of awareness. Specific afferent discharges may be elicited from the acoustic and occipital cortex of the cat under barbiturate anaesthesia, but the power of discrimination between different forms of stimulation is evidently absent. There is evidence additional to the ill-defined psychological concomitants of the K-complex to indicate that the brain in this situation behaves as a crude instrument. Its threshold for stimulation is high, its latency and refractory period long, and even at stimulus frequencies that would be relatively slow for excitation of specific sensory pathways responses are inconsistent or fail to be evoked altogether (fig. 6).

The *identity in the form of the K-complex for different modalities of stimulation* may thus be accounted for in terms of independent evidence indicating that it is the correlate of a crude perceptual process appropriate to a rudimentary state of awareness. Moreover since the response subserves no specific perception its *diffuse distribution* is also consistent with this evidence since it suggests the cerebral cortex behaves in this situation as one large undifferentiated sensory area.

Finally the three components present a sequence similar in some respects to that appearing in specific sensory areas following peripheral stimulation. As in the latter an electro-positive deflection is the initial change; there follows a bi- or tri-phasic sharp wave and then a slow after discharge. The resemblance to the phenomena associated with specific afferent stimulation is obviously a crude one and cannot be pressed too far. But it is clear that the hypothesis that the K-complex is a correlate of a crude perception and tends to initiate arousal in primitive states of vigilance, accounts for known facts about the phenomenon in a reasonably satisfactory manner. Moreover certain consequences flow from it which may be tested experimentally.

The time scale is, of course, quite different.

## SUMMARY

1. A study has been made of the morphological features of the K-complex during consciousness, sleep, and barbiturate anaesthesia, in 80 psychiatric patients and 15 normal subjects. No differences between the two groups of subjects came to light. During consciousness the phenomenon is elicitable in about 20 per cent of subjects but is prominent only in about one-third of these.

2. To the "sharp wave" component, the only one clearly discernible in the awake subject, there are added in unconsciousness one or more high voltage slow waves followed by a burst of "spindles". Both the latency and the duration of the sharp wave component are increased during sleep and barbiturate anaesthesia. In these and other states of diminished awareness the phenomenon is universally present; it is abolished in deep unconsciousness.

3. Evidence is presented suggesting that the K-complex is specially adapted for responding to transient disturbances in the environment. Swift adaptation occurs to continual stimuli; those given at shorter than 2-3 sec. intervals in sleep are interpreted as continual. Different forms of stimulation evoke identical K-complexes.

4. Studies of the voltage distribution of the K-complex by a special technique reveal congruent distributions during both first and second components which are consistent with the activity of a stationary source or sources. The widespread distribution of these two phases is hence attributed to their being mediated by some diffuse projection system to the cerebral cortex.

5. Attention is drawn to the similarities between the K-complex with its initial electropositive deflection and after-discharge, and the localised changes of smaller voltage evoked in specific sensory areas by various types of afferent stimulation. The K-complex is however distributed over a diffuse area and is identical for different stimuli. There is evidence to suggest that it is the correlate of a crude perceptual process which tends to initiate arousal. Such a theory satisfactorily accounts for the known facts about the complex: its non-specificity, diffuse distribution, and its presence in prominent form only in states of inconsciousness.


We are indebted to the Research Committee of the South-West Metropolitan Regional Hospital Board for financial support, and to Dr. Joshua Carse, Medical Superintendent, for his help and co-operation.

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# A NEW METHOD FOR MEASURING CEREBRAL BLOOD FLOW IN RELATION TO THE ELECTROENCEPHALOGRAM [1]

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Increasing evidence indicates that an intimate correlation exists between the cerebral blood flow and the electrical activity of the cortex (Schmidt and Hendrix 1938; Jasper and Erickson 1941; Darrow *et al.* 1944; Ingvar 1955). For a further study of this correlation it is a necessary requirement to measure the cerebral blood flow with a continuous method of sufficient accuracy. In spite of the numerous existing methods for the study of cerebral circulation, there are few, however, which will be suitable for concomitant studies of cerebral blood flow during rapid general changes of cortical electrical activity. The very accurate methods of Kety and Schmidt (1945, 1948), Lassen and Munck (1955), Nylin and Blömer (1955) as well as other methods according to similar principles do not permit a study of such changes since they are not continuous. The *Thermostrohmuhr* of Rein (1929) is not suited for smaller cerebral vessels in experimental animals. Heated thermocouples (Gibbs 1933; Serota and Gerard 1938) do not give pure expressions of circulatory changes only and they may easily imply damage to the cerebral tissue thereby altering circulation locally. Photoelectrical methods (cf. Kramer 1950, 1952; Darrow and Graf 1945) have also been used. Valuable direct observations on the cortical surface have been made with the "cranial window" technique (Forbes 1928) combined with measurements of pial vessels with the aid of a microscope (Forbes and Wolff 1928; Fog 1934). All optical methods, however, offer considerable difficulties for calibration.

In experimental animals circulatory conditions of various organs may be studied quantitatively with a high accuracy by measuring the outflow from a cannula inserted into a vessel (Gaddum 1929) and registering the intervals between the blood drops by means of an ordinate recorder (Fleisch 1930; Clemenz and Ryberg 1949). For extensive reviews of applications and improvements of this method see Folkow (1955) and Lindgren (1955).

In order to study cerebral circulatory conditions we have inserted a polyethylene tube into the superior sagittal sinus in cats and thus it has been possible to measure continuously the flow from rostral and parietal parts of the brain. Using this method and simultaneous EEG recordings we have been able to measure the alterations of cerebral vascular resistance concomitant with general EEG changes. A preliminary report on the method and the results has been published elsewhere (Ingvar and Söderberg 1956a).

## METHODS

Mature cats have been used. They were generally anaesthetized with Nembutal (40 mg/kg. intraperitoneally). Some experiments were carried out under Pentothal-curare, local anesthesia and artificial respiration.

A bony defect of about 5 mm. width was made over the superior sagittal sinus stretching from the occipital suture to the level of the gyrus proreus. Most of the anastomoses between the sinus and the diploic veins were interrupted by the craniotomy. Great care was taken not to injure the dura. In a few control experiments, however, the dura was cut along the sinus in order to exclude influence from the dural circulation. This did not alter the results obtained. Bony bleedings were stopped with bone wax and those from the sinus at the site of the interrupted anastomoses with Spongostan (Gelfoam). The animal was then heparinized.[2] About 10 min.

[1] This work has been supported by a grant from the fund for Medical Research, Karolinska Institutet, Stockholm.

[2] The Heparin was kindly placed at our disposal by the A. B. Vitrum, Stockholm.

later a ligature was placed around the sinus by means of a small bent needle 5 to 10 mm. anterior to the occipital suture. Immediately rostral to the ligature a small incision was made into the sinus and a polyethylene tube (outer diameter about 2 mm.) was inserted. A second ligature was generally made around the sinus to prohibit leakage and to keep the tube in place.

In order to be sure that no larger collaterals still existed after the craniotomy Ringer's solution was injected through the cannula in order to assess the resistance to inflow. If larger collaterals were still present

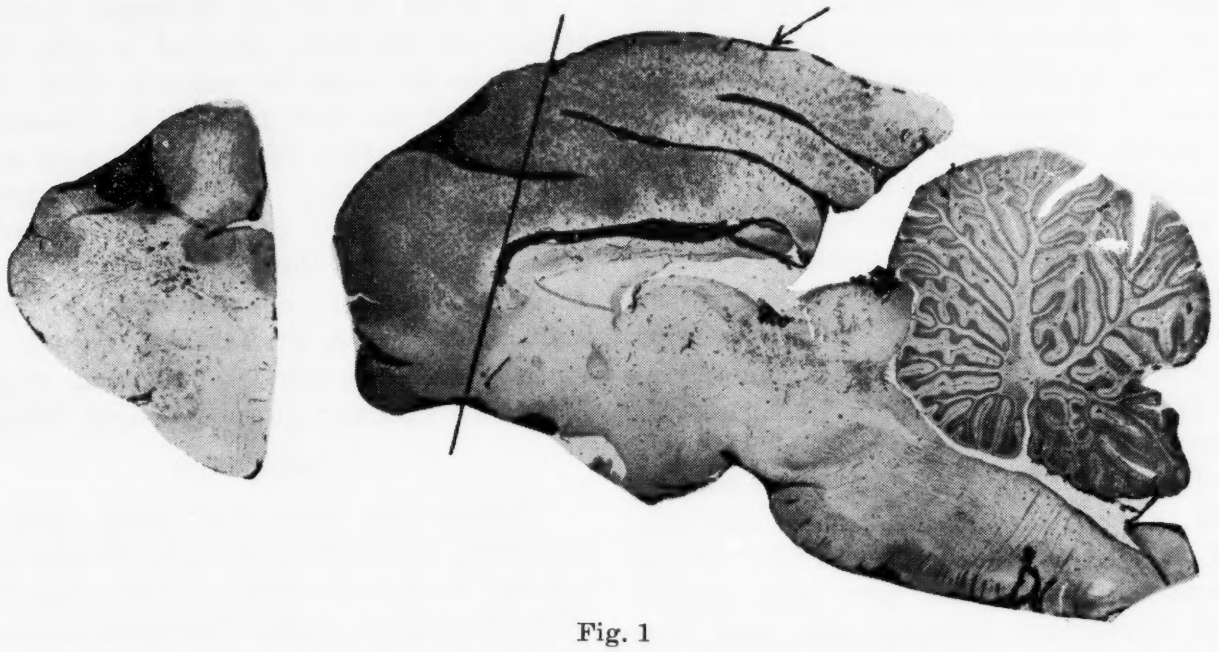

Fig. 1

Frontal and parasagittal sections of a cat's brain. Frozen sections after formalin fixation mounted in balsam after alcohol dehydration and xylene. Arrow indicates point of insertion of polyethylene cannula into the superior sagittal sinus. Line marks position of frontal section. India ink with 5 per cent gelatine has been injected through the cannula under high pressure. The major parts of frontal and parietal cortex have been stained.

the fluid could easily be introduced since there are no venous valves in the superior sagittal sinus. In such cases some further bony removal was carried out until the resistance to further injections was high. A special study was made with India ink injections through the tube in order to delineate the part of the cerebrum drained by the cannulated sinus (fig. 1).

The blood was allowed to drip from the free end of the polyethylene tube. The drops fell on two silver pins making contact between the anode and the grid of a thyratron. Thus a signal was given to an interval recorder [1] operating a mirror galvanometer, an audio-amplifier and a loudspeaker. The blood was returned to the animal by intravenous drip infusion. The rate of the drip infusion was kept the same as that of the flow from the cannula.

Figure 5 demonstrates a record with slow drop frequency. Each drop of blood rapidly carries the spot of the mirror galvanometer from the base of the figure from which it returns at slower speed so that a steeply rising line is recorded. The length of these lines is thus directly proportional to the time interval between the drops. By joining the upper ends of the lines a curve inversely proportional to the blood flow is obtained (cf. calibration on the left of fig. 5).

In the present investigation the method has been used to study the cerebral circulation under constant venous pressure. This diminished effects from changes in the intrathoracic pressure (Valsalva mechanism). Changes due to muscular activity have also been eliminated in control experiments with a curarizing agent (Flaxedil) and artificial respiration. It should also be emphasized that

[1] Constructed by Dr. B. Frankenhaeuser and Mr. E. Persson.

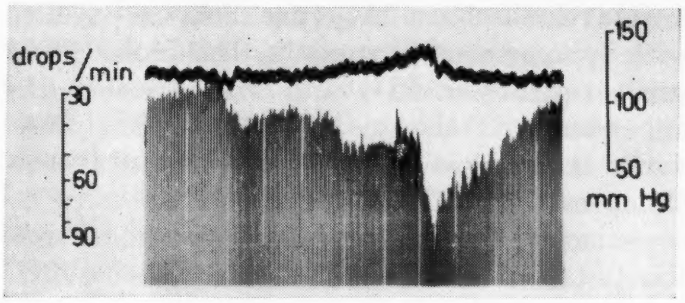


Fig. 2

Spontaneous variations in blood pressure (thick line) and cerebral blood flow in a lightly anesthetized cat (Nembutal). Length of the vertical lines is proportional to the interval between blood drops from the superior sagittal sinus. Note the large spontaneous increase of the flow which does not follow the slight changes in blood pressure and therefore represent a change of cerebral vascular resistance. Record is interrupted every 30 sec.

in the experiments reported here the normal intracranial pressure conditions have been altered by the craniotomy.

The blood pressure was recorded from the femoral artery by means of an *Elema* electromanometer operating a mirror galvanometer. Drugs administered were all injected intravenously through a cannula in the femoral vein.

The EEG was led off in bipolar leads from the middle suprasylvian gyrus and in some cases from the cruciate region. Small silver ball electrodes were used and they were mounted in drill holes. Two identical channels of AC amplification (consisting of an AC preamplifier with maximal gain of 60 db.

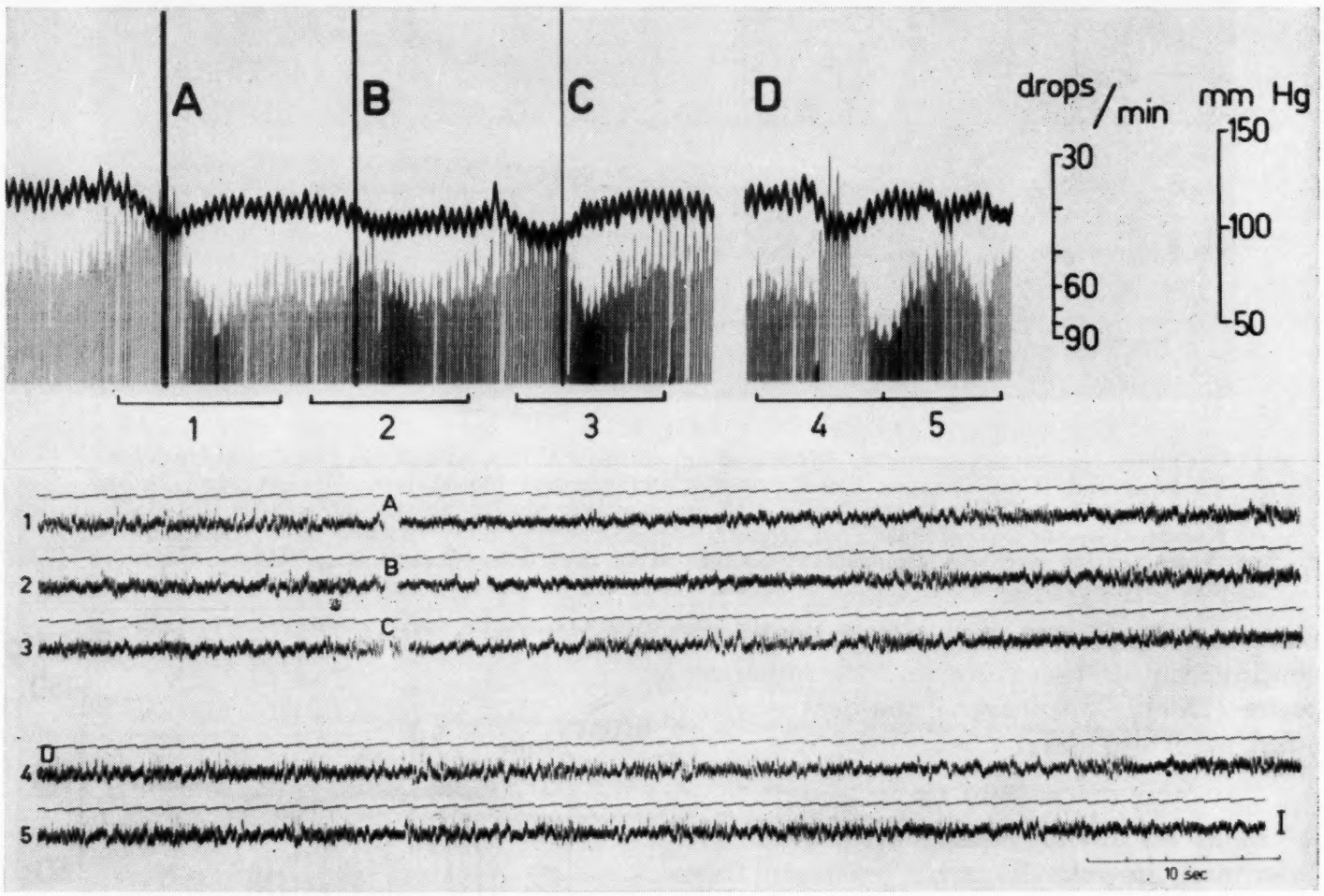


Fig. 3

Cat under light Nembutal anesthesia, Flaxedil and artificial respiration. Records of blood pressure, cerebral blood flow and EEG (middle suprasylvian gyrus). Horizontal lines below upper diagram indicates the periods of time during which the corresponding EEG samples were taken. Interruptions of record in upper diagram every 30 sec. Above each EEG sample a saw-tooth line indicate blood drops from superior sagittal sinus. A, pinching left fore-paw. B, twisting the pinna. C, 5 $\gamma$ adrenaline intravenously. Note increase of blood flow in A, B and C; in A and C accompanied by a slight increase of blood pressure, in B by a slight decrease of pressure. In A, B and C immediate electrographic arousal periods (1, 2 and 3). The increased flow in A, B and C has a latency of 5-10 sec. D, (later during the experiment) spontaneous changes of the blood pressure, cerebral blood flow and EEG.

and a DC main amplifier with maximal gain of 90 db.) were provided for recording the cortical activity. The inputs of the amplifiers were differential. A time constant of 0.2 sec. was used and a high frequency cut off at 10 kc. The amplifiers operated two beams on a cathode ray oscilloscope. During the experiment the animal's head was fixed in a stereotaxic device. The body temperature was continuously followed by an electrothermometer (Ellab, Copenhagen) and heat was applied when necessary.

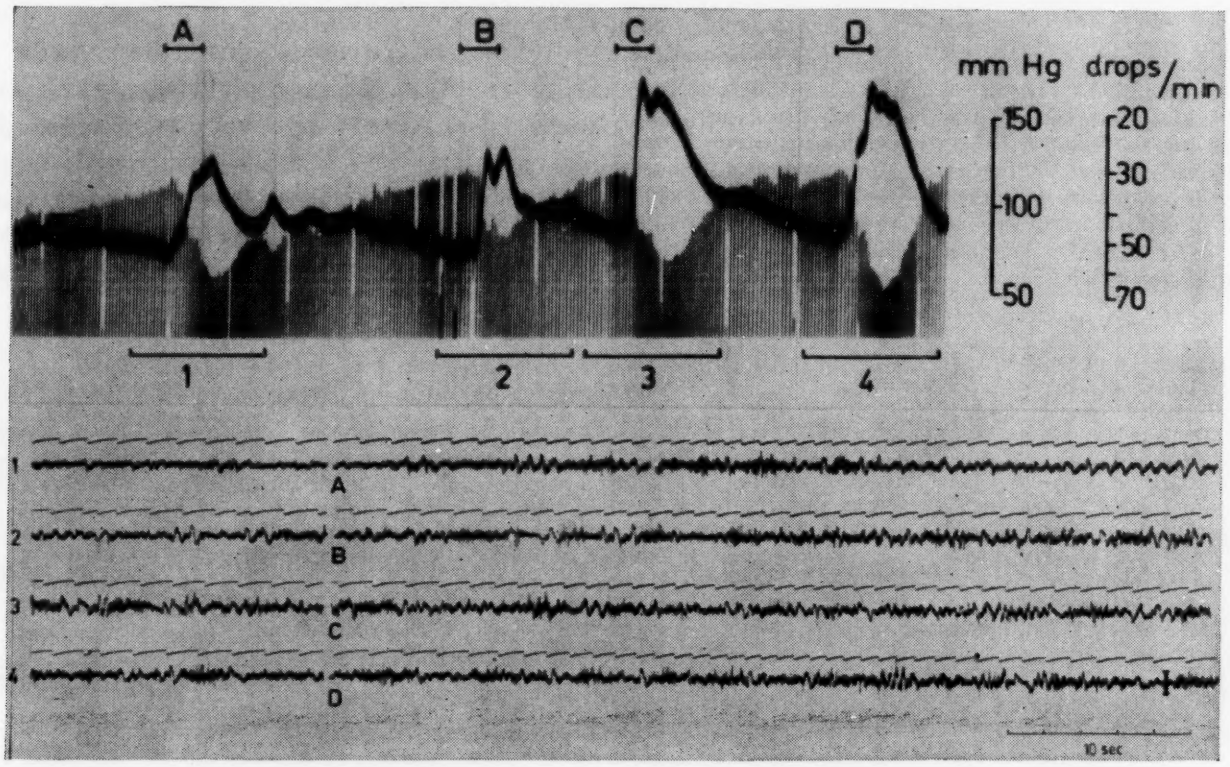


Fig. 4

Cat under Nembutal anesthesia. Effects of adrenaline (A 10 $\gamma$ and D 25$\gamma$) and noradrenaline (B 25 $\gamma$ and C 50 $\gamma$) upon blood pressure and cerebral blood flow. Effects upon blood pressure in A and B are comparable with one another, and so are the effects in C and D. Less increase of cerebral blood flow from noradrenaline (B and C). Concomitant EEG samples (indicated by numbers) demonstrate changes after first dose of each drug. Upper diagram interrupted every 30 sec.

## RESULTS

*Light anesthesia.* Most observations have been made in animals partly recovered from the initial anesthesia.

Earlier observations on the cerebral blood flow have generally stressed the constancy of the flow. With the present method we have found, however, that in the lightly anesthetized animal very marked "spontaneous" changes of the cerebral blood flow may occur. Such changes must be dependent upon rather vivid alterations in the vascular resistance of brain vessels since they are not in parallel with spontaneous changes in the blood pressure (fig. 2 and 3D) and may even be independent. It should be recalled that Bonvallet *et al.* (1954) have reported spontaneous changes in the EEG and blood pressure in experimental animals under conditions similar to those described above (see Discussion).

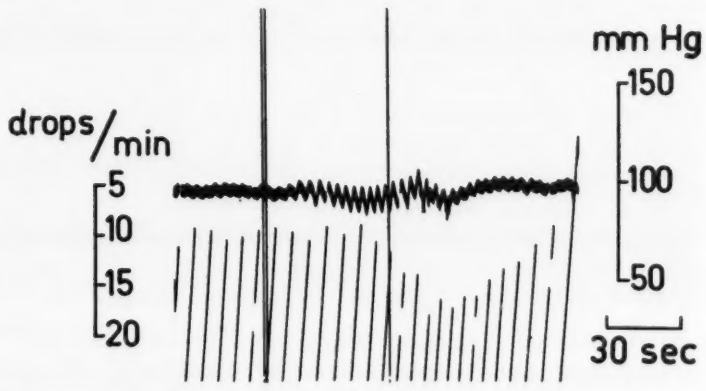


Fig. 5

Cat under Nembutal anesthesia. Sinus nerves, cervical sympathetic trunks and vagi divided bilaterally. Record of blood pressure and cerebral blood flow. Between marks inhalation of about 10 per cent $CO_2$ in oxygen. There follows a period of decreased cerebral vascular resistance. In blood pressure record variations due to hyperpnoea are seen.

In the lightly anesthetized animal various arousing stimuli such as pinching the paw or the nose, twisting the pinna and injecting small doses of adrenaline intravenously, all caused marked increase in the cerebral blood flow concomitant with transient activation of the EEG consisting of a general increase of frequencies and a diminution of amplitude (fig. 3). The increase of the flow must depend upon a vasodilatation since the blood pressure may be unaffected and even decreased during the periods of increased flow (fig. 3B). From the records it appears that the vasodilatation during arousal develops 5 to 10 sec. after the onset of the stimulus. In no instance during arousing stimulation was it observed that the vascular events preceded the changes in the EEG. In figure 3D spon-

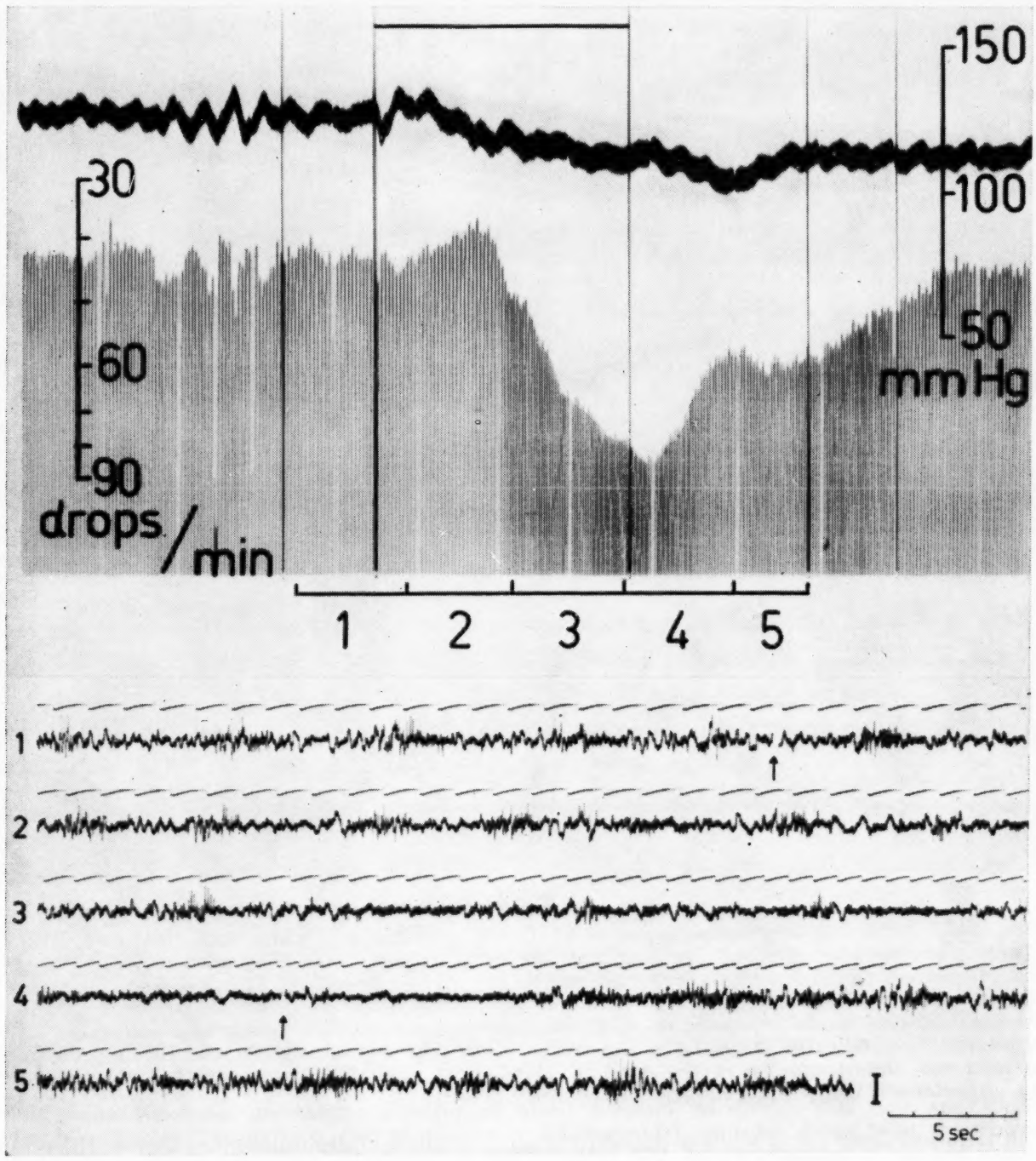


Fig. 6

Cat under Nembutal anesthesia. Records of blood pressure, cerebral blood flow and EEG (middle suprasylvian gyrus) before, during and after a short period of $CO_2$ inhalation (about 10 per cent $CO_2$ in oxygen). Upper horizontal bar and arrows in EEG tracings correspond to the period of $CO_2$ inhalation. In EEG samples 3 and 4 a period of EEG activation is seen, which is concomitant with a marked increase in the cerebral blood flow. Saw-tooth line in EEG tracings indicates drops from the sinus. Upper diagram interrupted every 30 sec.

taneous changes in the cerebral blood flow are demonstrated together with the simultaneous EEG record.

We have also studied the arousal reaction of the EEG induced by high frequency (200 c/sec.) electrical stimulation of the reticular activating system of the brain stem (Moruzzi and Magoun 1949). The effects upon

giving blood pressure effects of the same magnitude as adrenaline caused less increase in blood flow, indicating a vasoconstricting action of noradrenaline (fig. 4B and C). These two compounds also induce clear changes in the EEG (fig. 4, A and B) but frequent administration seems to diminish the effects (fig. 4, C and D).

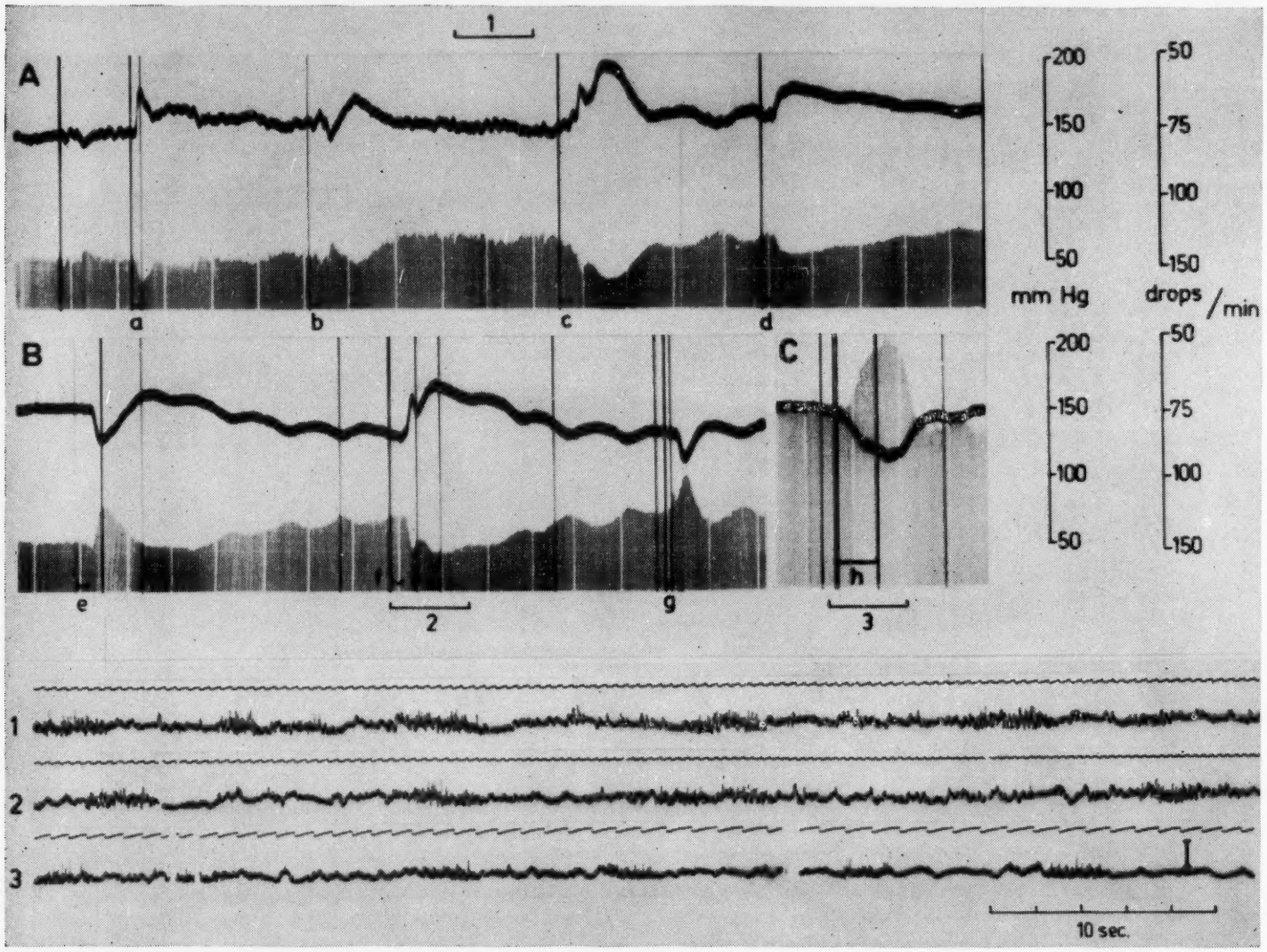


Fig. 7

Cat, deep Nembutal anesthesia. Records of blood pressure, cerebral blood flow and EEG (middle suprasylvian gyrus); (a) pinching the left fore-paw; (b) 25 $\gamma$ adrenaline, (c) 5 $\gamma$ noradrenaline, (d) 0.5 mg. dihydro-ergotamine, (e) 25 $\gamma$ adrenaline, (f) 5 $\gamma$ noradrenaline, (g) pinching the left fore-paw, (h) (after 20 min.) inhalation of about 10 per cent $CO_2$ in oxygen. Horizontal bars numbered 1, 2 and 3 correspond to EEG samples above which a saw-tooth line indicates drops from the sinus. Note that any change in the blood pressure is mirrored almost exactly in the cerebral blood flow. The EEG was constant throughout the experiment. Upper diagram interrupted every 30 sec.

the cerebral blood flow from such a procedure will be dealt with in detail in a forthcoming publication (Ingvar and Söderberg 1956b).

The increased flow obtained by adrenaline in larger doses seems proportional to the rise of the systemic blood pressure (fig. 4A and D). Noradrenaline, on the other hand, in doses

Figure 5 demonstrates the well-known cerebral vasodilatation from an increased $CO_2$ content of the blood. This experiment was carried out in a preparation in which the vagi, the cervical sympathetic trunks and the sinus nerves had been sectioned bilaterally. In a normal animal (fig. 6) $CO_2$ inhalation pro-

duced the same effect. There was in this case a change in the EEG from the usual barbiturate pattern with spindles into an activated type concomitant with the vasodilatation.

changed by various procedures such as pinching the foot, injection of adrenaline and noradrenaline, before and after dihydro- ergotamine (cf. Ingvar and Söderberg 1956b). Inhalation of $CO_2$, was also tested after the

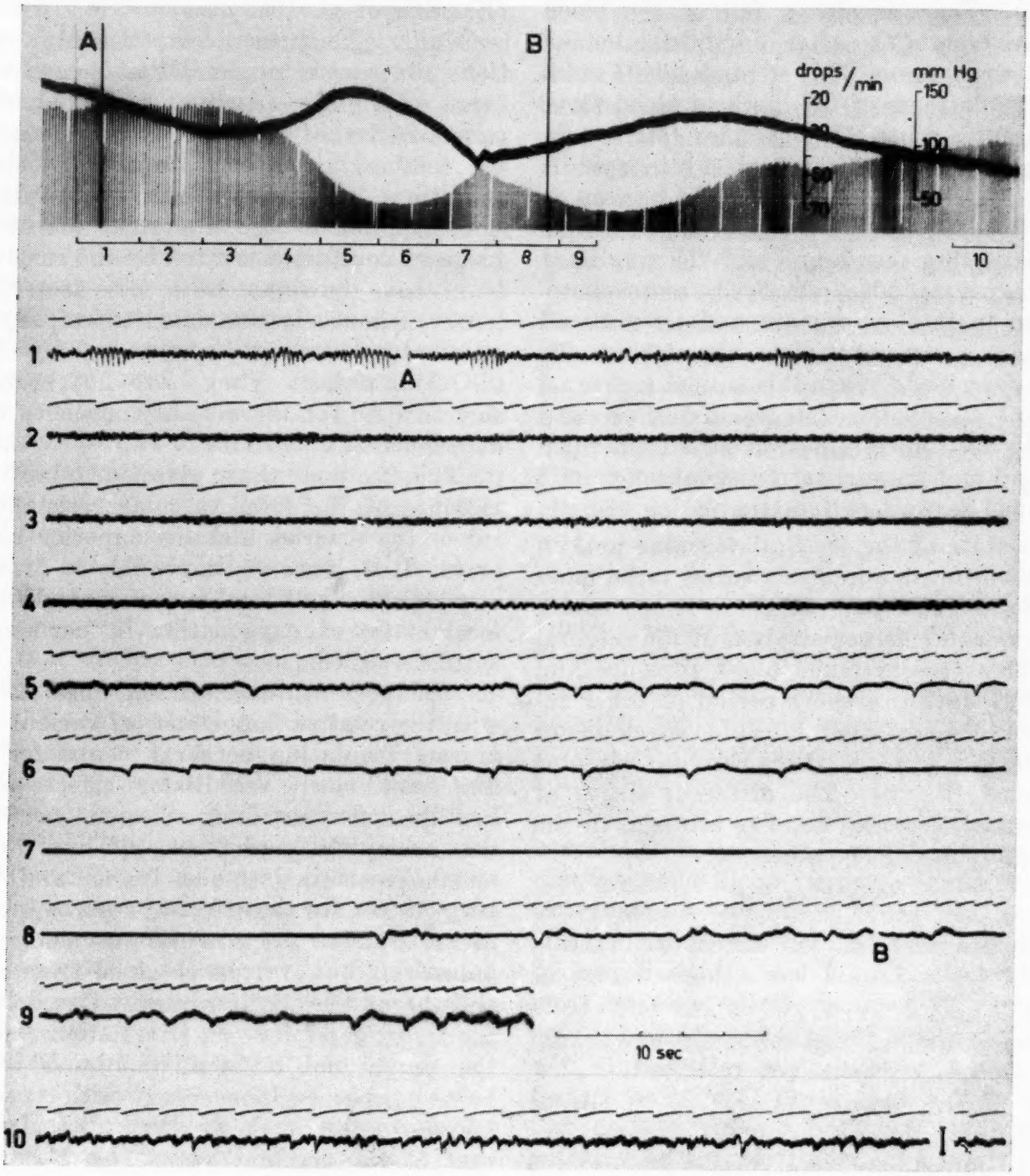


Fig. 8

Cat under Nembutal anesthesia. Records of blood pressure, cerebral blood flow and EEG (middle suprasylvian gyrus). Saw-tooth line in EEG samples indicates drops from the sinus. Between A and B ether was introduced in the inspired air. Ether produced a marked vasodilatation which outlasted the period of inhalation. Upper record is interrupted every 30 sec.

*Deep anesthesia.* In deep anesthesia the cerebral vascular resistance is constant and thus the flow measured from the sinus is a direct function of the systemic blood pressure. In figure 7 the blood pressure has been

administration of dihydro-ergotamine. It is obvious that the changes in the cerebral blood flow throughout these procedures were proportional to the blood pressure changes.

Apart from the well-known reversal of the

effect of adrenaline (Dale 1906) and of paw-pinching upon the blood pressure after dihydro-ergotamine, it should also be observed that dihydro-ergotamine completely abolishes the vasodilator effect of increased $CO_2$ inhalation. There is also a fall of the blood pressure from $CO_2$ after administration of dihydro-ergotamine (Liljestrand 1948) with a passive decrease of the cerebral blood flow. The accompanying EEG samples (fig.7, 1-3) demonstrate the typical barbiturate spindle pattern in which no changes could be seen to result from any of the procedures mentioned. The nictitating membrane and the pupillary diameter were also observed and photographed in this experiment and were found to be in a constant state throughout the period described. When this animal recovered from the anesthetic, changes in the cerebral vascular resistance appeared at a time when the pupil and the nictitating membrane again responded to nociceptive stimulation.

The state of the cerebral vascular tone in deep barbiturate anesthesia seems to be more constricted than that which develops under ether. Continuous registration of the cerebral blood flow, the systemic blood pressure and the EEG during a short period of ether inhalation demonstrated a rapid development of a marked decrease of the cerebral vascular resistance (fig. 8). The different stages of the cortical electrical activity are seen in the accompanying EEG records.

## DISCUSSION

The results presented above demonstrate that the method used has a high degree of accuracy. This is especially evident from figure 7 in which the slightest changes in systemic blood pressure are reflected in the record of the sinus blood flow. The control experiments described under "Methods" clearly showed that the flow studied pertains to the whole rostral part and some of the parietal parts of the cat's brain, thus giving a measure of circulatory conditions in those areas of the cortex in which general EEG changes were studied.

We are aware that the operative procedure has only interrupted the major part of the anastomoses between the brain and extracerebral vascular systems. Anastomoses in the region of the olfactory bulbs and to the orbital veins have not been eliminated but are probably of minor importance. Even the jugular bulbs in man are known to hold only 2.6 per cent blood of extra-cerebral origin (Shenkin *et al.* 1948).

Under the present experimental conditions the venous pressure has been constant (zero or slightly negative) and it should be emphasized that a factor of importance for the cerebral circulation under physiological conditions has thereby been excluded. The same applies to the abnormal intracranial pressure conditions created by the removal of bone above the sinus. Both these factors, can, however, be easily controlled technically by a closed drop recording system and by closing the skull defect. They have not been considered here for the sake of simplicity of the experimental conditions.

The method thus gives a quantitative measure of the total vascular resistance between the arteries and the superior sagittal sinus. It is, however, impossible to draw any conclusions about local vascular conditions or local states of oxygenation in parts of the system studied.

The present investigation does not deal with the relative importance of various mechanisms regulating cerebral vasomotor tone. The well-known vasodilator effect of $CO_2$ and the vasoconstrictor effect of noradrenaline exemplify mechanisms of humoral and metabolic origin (see also Ingvar and Söderberg, 1956b, for the effect of ergotamine). No direct evidence for a neural vasomotor mechanism can, however, be obtained from our results here. The shortest latency found (2 sec.) for a change of flow on stimulation (twisting the pinna and nociceptive stimuli) would, however, not be inconsistent with vasomotor nerve activity such as demonstrated in the case of the cerebral vessels by Forbes and Wolff (1928), Chorobski and Penfield (1932), Fog (1934) and Darrow *et al.* (1944).

The "spontaneous" changes of the cerebral blood flow and systemic blood pressure in lightly anesthetized preparations have been observed to be related to concomitant periods of arousal in the EEG. It was pointed out above that the changes of EEG and blood pressure are probably identical to similar

events described by Bonvallet *et al.* (1954). It seems reasonable to assume that they represent variations in the state of wakefulness of the animal due to the experimental conditions which by necessity must imply exteroceptive stimulation. It was, for instance, observed that less frequent changes appeared in the flow and EEG when the laboratory was silent.

In all the experiments with exteroceptive stimulation it has been observed that the change of EEG — the activation — precedes the cerebral vascular events. This would seem to be an expression of a vasomotor mechanism maintaining homeostasis during changes in cerebral neuronal activity. On the other hand, active changes in the cerebral vascular resistance induced by e.g. atropine or $CO_2$, under certain conditions may give rise primarily to changes of the cerebral blood flow and secondarily to changes in the EEG (Ingvar and Söderberg 1956b). The possibility of influencing the electrical activity of the cortex by an active change of the cerebral vasomotor tone therefore also seems to exist.

It has previously been reported (Ingvar 1955) that during electrical arousal induced by brain stem stimulation the electrical activity of a neuronal isolated part of the cortex may be altered. From microscopical observation of the cortical surface it was found that the circulation in the pial vessels is increased in arousal. The present demonstration of the magnitude of such changes is in strongly support of the assumption made earlier that the effects upon the activity of isolated cortex could be caused by changes in circulation.

When using multiple EEG leads simultaneously we found that the correlation between cerebral blood flow and EEG in the arousal reaction was not uniform. It appeared more striking in some areas than in others, a fact which is to be expected since in the lightly anesthetized state there are great differences in the electrical activity in different cortical areas. As was stated above, the method of measuring the blood flow does not permit conclusions on local circulatory changes in the system studied, and it is therefore not possible to conclude whether local differences in the EEG arousal reaction correspond to local differences in blood flow changes.

Autonomic mechanisms are, in general, very sensitive to anesthesia. Schneider and Schneider (1934), among others, have previously demonstrated the effect of anesthetics upon cerebral vasomotor mechanisms. Our observations indicate that these mechanisms are as sensitive to anesthetic agents as, for example, those regulating the pupillary diameter, the tone of the nictitating membrane and the tone of cutaneous vessels (Ingvar and Söderberg 1956b). The cutaneous vasomotor tone, on the other hand, seems to be regulated in an inverse manner since there is, as a rule, a cutaneous vasoconstriction during arousal (von Euler and Söderberg 1956). There are, however, some autonomic mechanisms such as those regulating systemic blood pressure which seem less sensitive to anesthesia. They may even in deep anesthesia be influenced by nociceptive stimulation without an arousal reaction in the EEG and with only passive changes in the cerebral blood flow.

## SUMMARY

1. A new method is described for continuous measurement of the cerebral blood flow in the cat. The method employs the registration of the flow from the cannulated superior sagittal sinus after elimination of the main anastomoses between the sinus and extracerebral vessels.

2. The method has been used to study the correlation between cerebral blood flow, EEG and systemic blood pressure under varying experimental conditions such as arousing stimulation, anesthesia, and administration of drugs.

3. The results confirm that an intimate correlation exists between cerebral vasomotor tone and cortical excitatory state as reflected in the EEG. Thus, arousing stimuli which activate the EEG give a marked increase in the cerebral blood flow which is independent of the changes of the systemic blood pressure.

Spontaneous changes of flow accompanied by general changes of the EEG have also been observed to occur in the lightly anesthetized animal.

4. Small doses of anesthetic agents, sufficient to induce a sleep pattern of the EEG and a block of the arousal reaction, paralyze the mechanisms regulating cerebral vasomotor

tone. In barbiturate anesthesia the cerebral vessels are more constricted than under ether.

5. While confirming earlier findings on cerebral circulation, the results, in addition, demonstrate that the cerebral vascular resistance undergoes larger changes than have previously been shown. The results also throw new light on the importance of autonomic mechanisms for the regulation of sleep and wakefulness.

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# THE ROLE OF THE SINO-AORTIC RECEPTORS IN THE ACTION OF ADRENALINE, NOR-ADRENALINE AND ACETYLCHOLINE ON THE CEREBRAL CORTEX [1] [2]

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Earlier work indicates that an increase of the blood pressure produced by drugs (adrenaline, nor-adrenaline) or by mechanical means reduces the excitability of autonomic sympathetic centers. Thus the pressor response and the contraction of the nictitating membrane (NM) which follows the stimulation of the brachial plexus is lessened if this stimulus is applied while the blood pressure has been raised by the injection of adrenaline (Darrow and Gellhorn 1939). Similarly it was found that the sympathetic effects of stimulation of the posterior hypothalamus were lessened during the adrenaline-induced hypertension (Gellhorn 1941). Whereas the centrally induced excitation is diminished under these conditions, the excitability of the peripheral end of the cervical sympathetic remains unaltered. Similarly Malmejac, Chardon and Neverre (1951) showed in ingenious anastomosis experiments that adrenaline inhibits the tonic function of the autonomic centers causing adrenomedullary secretion whereas it exerts the opposite effect on the gland itself. Gellhorn, Yesinick, Kessler and Hailman (1942) showed further that variations of the systemic blood pressure and consequently of the sino-aortic pressure altered the reactivity of the somatic nervous system. This was disclosed by the fact that convulsions decreased when mechanically or through drug action the sino-aortic pressure was increased whereas convulsions were augmented while the sino-aortic pressure was lowered. More recently Bonvallet, Dell and Hiebel (1953) showed that distension of the carotid sinus reduces cortical activity.

These data and the experiments of Gellhorn, Redgate and Sigg (1952), which demonstrated that lowering of the sino-aortic pressure induced an increase in cortical excitability, suggest that sino-aortic pressor reflexes exert a profound influence on cortical excitability. In order to further investigate this relationship, experiments were performed on the action of hypertensive (adrenaline, nor-adrenaline) and hypotensive (acetylcholine) drugs on cortical potentials before and after the denervation of the sino-aortic area.

## METHODS

The experiments were performed on more than 30 cats which were prepared under light Pentothal anesthesia later supplemented by Intocostrin. The cortical potentials were recorded with an eight channel Grass apparatus from various areas through monopolar silver electrodes inserted into the skull so that they were in contact with the intact dura. The blood pressure was recorded from the femoral artery by means of a Hg. manometer and two selsyns. The potentials of one channel were continually analysed with an Offner analyzer. If the results of the analyses are presented in graphs as in figures 2, 3, 5 and 6, the amplitude of every frequency which was recorded was averaged for 4-6 ten second periods and the changes which occurred after the administration of adrenaline, nor-adrenaline or acetylcholine were expressed in percentages of the controls. The carotid sinuses were carefully exposed and a ligature was placed under the carotid sinus nerves and the vagi. After

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the tests had been obtained in the normal animal, the nerves were severed and phenol was applied to the sinus area. This procedure was accompanied regularly by a marked rise of the blood pressure. The hypo- and hypertensive drugs were injected into the femoral vein. For further details on the utilization of the cortical analysis see below.

the appearance of grouped potentials of large amplitude similar to those appearing in barbiturate anesthesia. The appearance of these potentials is confined to the period of the adrenaline-induced hypertension. Record B shows that this action of adrenaline is lessened after a minute dose of Pentothal had been administered. With further application

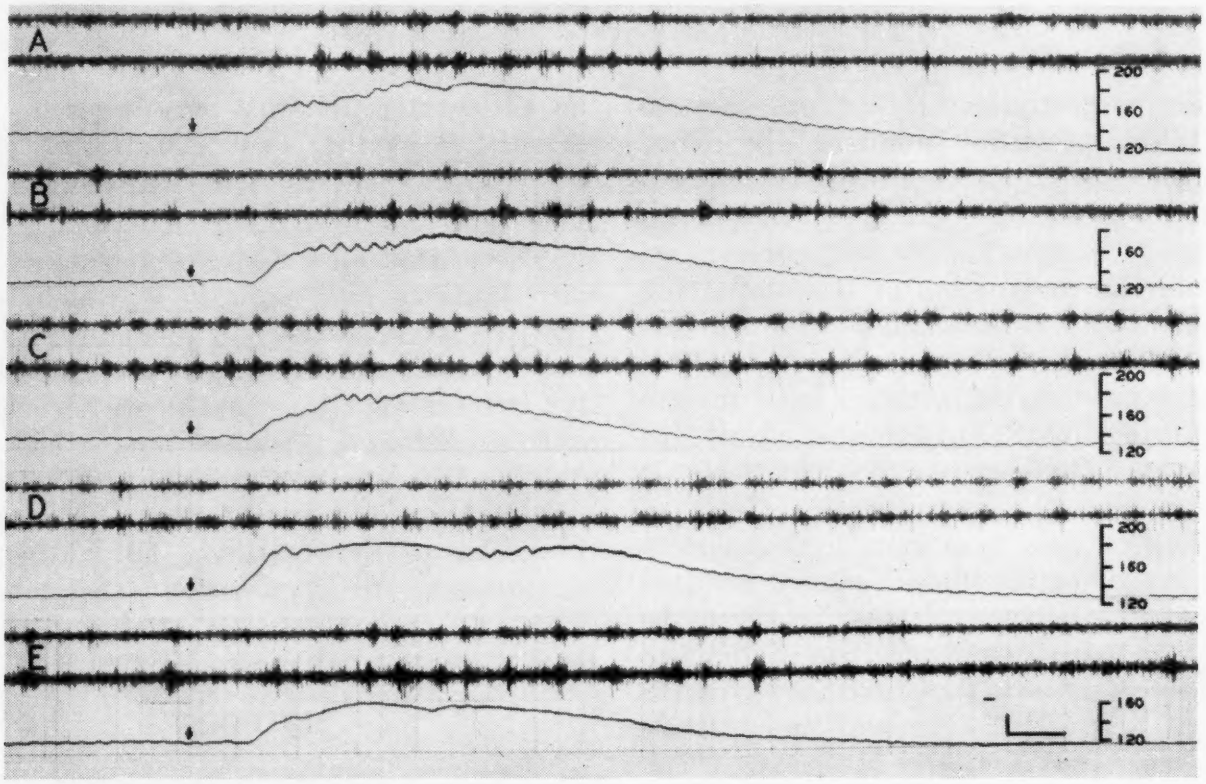


**Fig. 1**

Cat, 2.5 kg.
1. Gyrus proreus. 2. Gyrus suprasylvius anterior.
At arrows 4 gamma/kg. adrenaline i.v.

A. Control, 2:30 p.m.
2.8 mg/kg. sodium Pentothal i.v., 2:42 p.m.
B. 2:56 p.m.
2.8 mg/kg. Pentothal, 3:05 p.m.
C. 3:18 p.m.
Three times 2.8 mg/kg. Pentothal i.v. at 3:34, 3:50, and 4.13 p.m.
D. 4:18 p.m.
E. 6:30 p.m.

Calibration: 100 $\mu$V. and 10 sec.

## RESULTS

1. *The Effect of Adrenaline and Nor-adrenaline on the Potentials of the Cortex in Cats Before and After Sino-aortic Denervation.*

Figure 1 shows the effect of the injection of 4 gamma adrenaline/kg. on two cortical areas at varying degrees of barbiturate anesthesia. It is evident that in a very "light" cat whose EEG is characterized by fast potentials of a low amplitude adrenaline induces of Pentothal the grouped potentials become more frequent (C) and of lesser amplitude (D). Under these conditions adrenaline fails to alter the cortical potentials. Record E shows that as the effect of Pentothal wears off the characteristic action of adrenaline on the cortical potentials is restored. Similar results were obtained with nor-adrenaline.

In order to gain further insight into the changes of cortical potentials following the administration of adrenaline, experiments

were performed on the action of adrenaline and nor-adrenaline on cortical potentials before and after sino-aortic denervation. The potentials were subjected to a frequency analysis with the Offner analyser. The amplitude of the potentials of a given frequency which was recorded for a period of 10 sec. was averaged from 4 to 10 periods and the changes which occurred after the administration of adrenaline were expressed in percent-

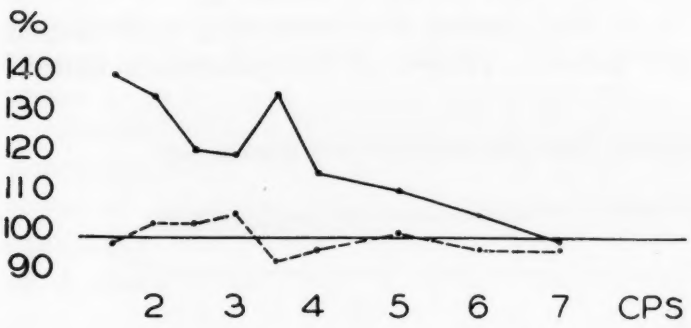


Fig. 2

The effect of 4-5 gamma/kg. adrenaline I.V. on the frequency analysis of the cortex of the cat before (———) and after (— — —) denervation of the sino-aortic area. The amplitudes of the control and experimental periods were averaged for each frequency (abscissa) and the numbers obtained in the experimental periods were expressed in percentages of the controls (ordinate). The graph shows an increase in the amplitude at low frequencies after adrenaline, an effect which is absent after sino-aortic denervation. This graph is based on experiments on 5 cats.

ages of the control values. Figure 2 shows a graph which is based on 5 experiments on 5 different cats in which the effect of 4 to 5 gamma adrenaline/kg. on cortical potentials was studied before (———) and after (— — —) sino-aortic denervation. Since no significant changes occurred with frequencies of 8-30/sec. the graph presents only the changes which occurred in the potentials of low frequencies. It may be inferred from figure 2 that there is a shift in the frequency spectrum to the lower frequencies and that this effect is absent after sino-aortic denervation.

Even more marked changes were seen after injection of small doses of nor-adrenaline. In the experiment of figure 3 the effect of nor-adrenaline (4 gamma/kg.) on potentials of varying frequencies is reversed after sino-aortic denervation. Before denervation nor-adrenaline increased the amplitude of potentials of low frequencies (between 2 and 9/sec.) and lowered the amplitude of the potentials of the frequencies 10 to 30/sec. After denervation, however, the opposite effect is produced by the injection of nor-adrenaline. Similar results were obtained in numerous other experiments. However, in several ani-

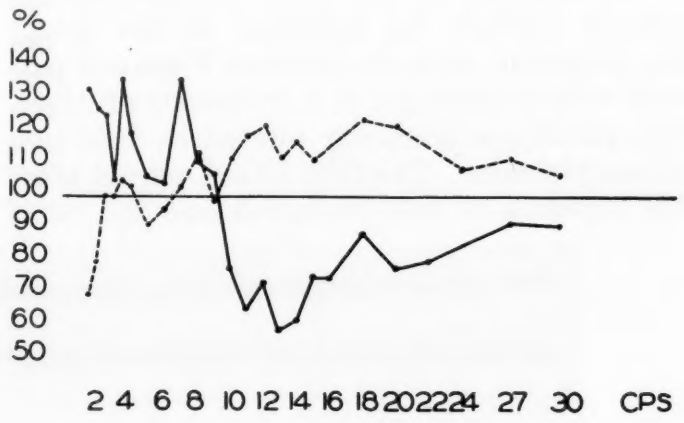


Fig. 3.

Cat, 2.25 kg.
Frequency analysis of the motor cortex. The effect of 4 gamma/kg. nor-adrenaline i.v. Other details as in figure 2. Note that in the normal animal the amplitude of the potentials at low frequencies is increased and that of the high frequencies is diminished after administration of nor-adrenaline (———). After sino-aortic denervation (— — —), the effect of nor-adrenaline is reversed.

mals nor-adrenaline which exerted the typical effects described above in the normal cat failed to change the frequency spectrum after sino-aortic denervation.

2. *The Effect of Acetylcholine on Cortical Potentials and the Dependence of this Effect on Sino-aortic Receptors.*

Earlier work from this laboratory (Gellhorn, Redgate and Sigg 1952) had shown that the injection of hypotensive drugs (acetylcholine, mecholyl and histamine) leads to cortical excitation. Similar effects were obtained when through variations of the blood volume by means of a procedure described by Fog (1938) the blood pressure and consequently the sino-aortic pressure was lowered.[1] These observations suggest that baroreceptor reflexes may play a decisive part in the cortical excitation which occur when the pressure in the carotid sinus is lowered. The following experiments seem to justify this assumption.

Figure 4 illustrates a typical record of the action of 1.25 gamma/kg. of acetylcholine on cortical potentials. EEG records show mainly

[1] Unpublished work.

a reduction in the amplitude of the potentials during the hypotensive period. This effect is reversible and is later followed by the appearance of grouped potentials. From the study of the EEG analysis [1] the following data may be obtained:

1. Whereas in the two 10 sec. control periods (before the injection of the drug) the potentials show an inverted V-shaped pattern with a maximum at a frequency of 9/sec. this pattern is markedly altered on injection of acetylcholine. The first 10 sec. period after the injection is still unaltered and the blood pressure does not begin to fall until the end of this period. During the following 2 periods the blood pressure reaches its minimum and then begins to return towards its original level. These 2 periods show a clear shift of the maximal amplitude to the higher frequencies (15 and 16/sec.). This shift persists during the last periods of record A. On close inspection it is noted that these changes are accompanied by a marked reduction in the amplitude of the potentials in the first three groups (frequency 1.5 to 13/sec.) and this effect reaches its maximum in the 2nd to the last period of record A.

2. The record B (continuous with record A) shows a return of the potentials and of the frequency pattern to the control level. The pattern seen in the last period of record A is intermediate between that produced by the injection of acetylcholine and that recorded in the pre- and post-injection control periods.

3. Although the frequency pattern of record B is similar to that seen in the control periods of record A, the amplitude of the potentials is slightly increased. This is accounted for by the occurrence of rather marked grouped potentials which were practically absent under control conditions.

The interpretation of these changes seems to be as follows. An excitatory effect char-

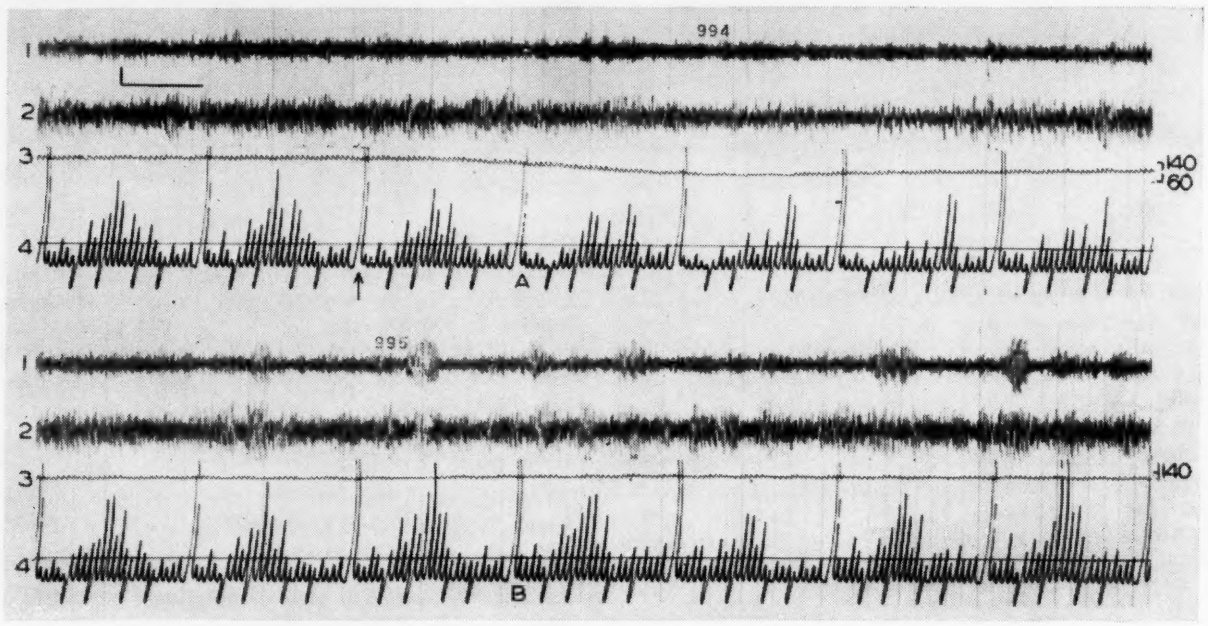


**Fig. 4**

Cat, 4 kg.
1. Left motor cortex
2. Left auditory cortex
3. Blood pressure
4. Analysis of the motor cortex

A and B are continuous records. At the arrow 1.25 gamma/kg. acetylcholine i.v.
Calibration: 50 $\mu$V. and 5 sec.

[1] The record showing the analysis consists of 10 sec. periods separated by large vertical deflections (''epoch markers''). The smaller deflections of the pen between the two epoch markers indicate the relative amplitude of the individual frequency components during this 10 sec. period. There are 4 downward deflections, so-called frequency band markers which divide the frequency spectrum into 5 groups. The pen deflection pips comprise the following frequencies/sec.:
1st group: 1.5, 2, 2.5, 3, 3.5
2nd group: 4 to 7
3rd group: 8 to 13
4th group: 14, 15, 16, 18
5th group: 20, 22, 24, 27, 30

acterized by a diminution in the amplitude of the analysed record at the lower frequencies and an increase of the amplitude at the higher frequencies up to 16/sec. occurs at the end of the hypotensive phase and particularly as the blood pressure returns to the pre-injection level. Then the frequency patterns return to that seen under control conditions. Such a phase may be followed as in the last two thirds of record B by an intensification of grouped potentials which lead to an increased amplitude of the analysed record but to no change in the frequency pattern. This phase seems to indicate a rebound phenomenon.

Similar effects of acetylcholine on cortical potentials were seen in numerous tests. It occurred not infrequently, however, that the excitatory effect was preceded by a phase of a marked decrease of the amplitude of

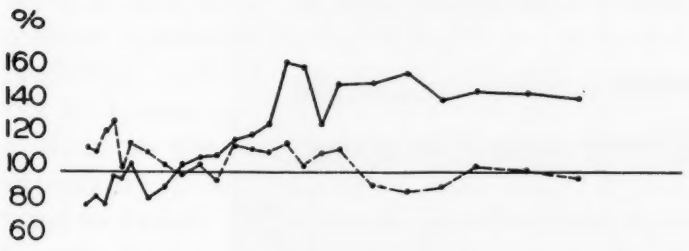


**Fig. 5**

Cat, 2.5 kg.
The effect of 2 gamma/kg. acetylcholine i.v. on the analysis of the occipital area. Acetylcholine increases the amplitude of the fast potentials in the normal animal (———), whereas no significant change occurs after sino-aortic denervation (— — —) on injection of 4 gamma/kg. acetylcholine.

potentials at all frequencies. This phase coincided with the period of greatest hypotension and was obviously related to the degree and duration of the hypotension.

Figures 5 and 6 illustrate the influence of sino-aortic denervation on the action of acetylcholine. Whereas this drug in a dose of 2 gamma/kg. (fig. 5) exerts a typical excitatory effect on the cortical potentials indicated by a marked increase in the amplitude of the potentials of a frequency of 10 to 30/sec. (———) it fails to alter the frequency spectrum after sino-aortic denervation (— — —) even when the dose is doubled.

The experiment represented in figure 6 shows a marked excitatory effect on injection of only 0.8 gamma/kg. acetylcholine. This excitatory action (———) appears as a reduction of the amplitude of the potentials of low frequencies and an increase of that of high frequencies. After sino-aortic denervation (———) this effect is greatly lessened or questionable.

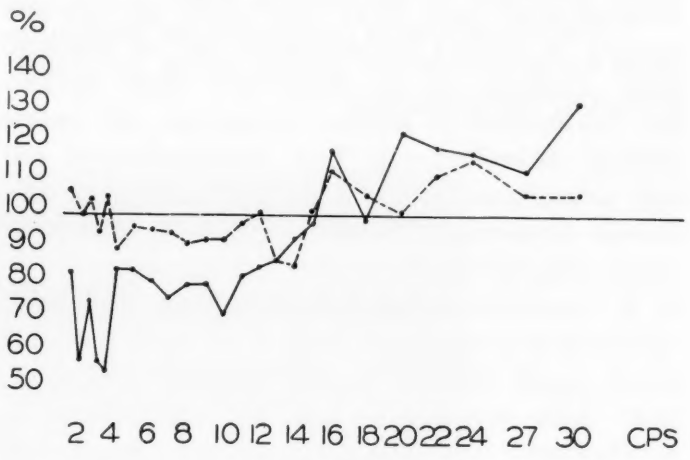


**Fig. 6**

Cat, 2.25 kg.
The effect of .8 gamma/kg. acetylcholine i.v. on the analysis of the motor cortex. Note that this drug causes a diminution in the amplitude of the potentials at low frequencies and an increase in the amplitude of the potentials of high frequencies in the normal animal (———), but no significant changes after sino-aortic denervation (— — —).

Finally (fig. 7), a record is presented in which acetylcholine was administered in large doses and the original records obtained with the analyser are shown together with the EEG record. A control period (before injection), the period showing the greatest change after the injection, and a period showing the recovery are illustrated for the normal and the sino-aortic denervated cat. A glance at the EEG records reveals that in B the potentials are increased in frequency and amplitude. The record of cortical frequency analysis shows that the amplitude of the slow potentials is diminished and that of the fast potentials is increased. In other words a marked excitation has taken place which coincides with a rise of the blood pressure (following the hypotensive phase) above the control level. In contrast, the records shown in D, E, F of figure 7 show the effect of twice as large a dose of acetylcholine to be rather weak after the denervation of the sino-aortic area. No clear changes appear in the EEG's. The analysed record shows in E a slight increase in the last group of potentials, but by no means the marked changes which half of the

dose of acetylcholine produced on the cortical potentials when the baroreceptors of the sino-aortic area were intact. There was also not a phase of overshooting blood pressure following the hypotensive action of acetylcholine but a slow and somewhat incomplete return of the blood pressure to the control level.

Other hypotensive drugs such as histamine exert an action on the cortex which is similar to that of acetylcholine.

conduction of the impulses to specific projection areas (Gellhorn 1953; French, Verzeano and Magoun 1953). The fact that this effect of adrenaline and nor-adrenaline alters the activity of the cortex as a whole supports the interpretation that the diffuse projection system to the cortex is involved. Our findings are also in agreement with experiments of Hiebel, Bonvallet and Dell (1954) on the action of adrenaline after chlorpromazine.

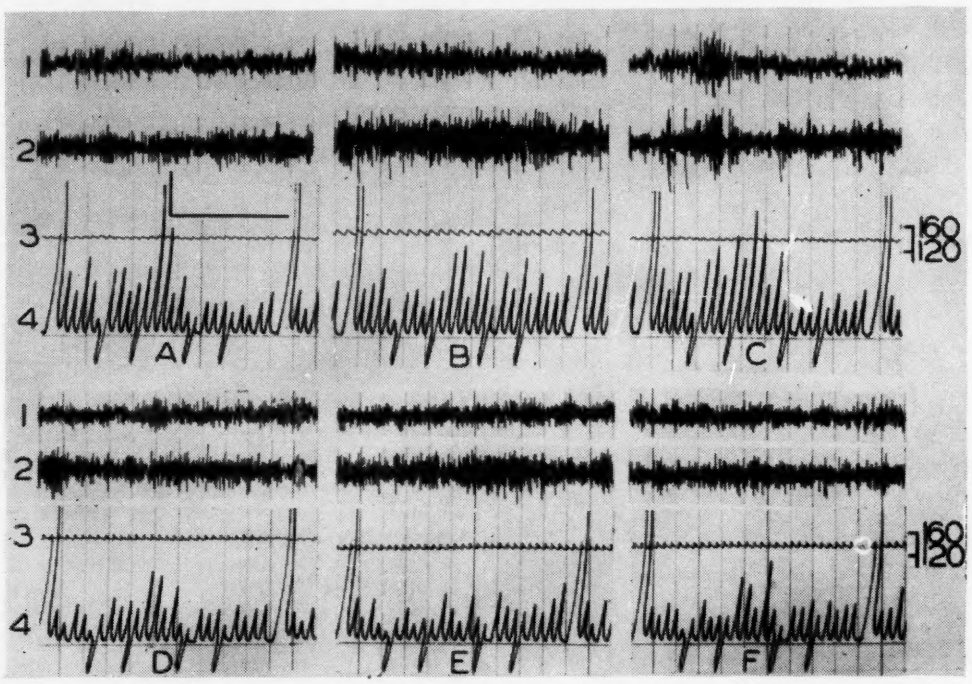


Fig. 7

Cat, 2.2 kg.
1. Bilateral motor cortex
2. Left motor to left occipital cortex
3. Blood pressure
4. Analysis of bilateral motor cortex
A. Control
B. Maximal effect 80 sec. after 20 gamma/kg. acetylcholine i.v.
C. One min. after B.
After C, denervation of the sino-aortic areas.
D. Control
E. 80 sec. after injection of 40 gamma/kg. acetylcholine i.v.
F. One min. after E.
Calibration: 50 $\mu$V. and 5 sec.

## DISCUSSION

There are two phenomena described in this paper which require a brief comment. The first refers to the fact that the changes induced in the EEG record by adrenaline or non-adrenaline are abolished by small quantities of barbiturates. This observation suggests that the action of adrenaline depends on the reticulo-hypothalamic-cortical system which is blocked by minute quantities of barbiturates which do not interfere with the

The second and chief phenomenon studied in this work is the demonstration of the influence of sino-aortic reflexes on cortical potentials. It was found that the excitatory action of acetylcholine and other hypotensive drugs as well as the inhibitory action of hypertensive drugs (nor-adrenaline and adrenaline) depends on the sino-aortic receptors. After the elimination of these receptors, the above named drugs exert in most cases (in the doses studied) no effect on the

cortex. In a few instances a reversal occurred in tests with nor-adrenaline: whereas in the intact animal this drug caused a slowing of the cortical potentials, a slight shift of the cortical frequency spectrum to the relatively fast potentials was noted after sino-aortic denervation. In these instances nor-adrenaline produces a slight excitatory action on the cortex after the sino-aortic denervation, but such an excitatory action was in general not seen in the intact animal.

How the baroreceptor impulses affect the cortex of the brain remains to be investigated in more detail. That the hypothalamus is involved is suggested by the work of Darrow and Gellhorn (1939) who found that the excitability of the posterior hypothalamus is lessened by the intravenous injection of small amounts of adrenaline. Recent, unpublished work in this laboratory indicates that the frequency spectrum of hypothalamic potentials is shifted toward the low frequencies under the influence of hypertensive drugs whereas a shift to the higher frequencies occurs on injection of acetylcholine and other hypotensive drugs. The excitatory action of hypotensive drugs on the hypothalamus has also been shown after strychninization of this structure. The frequency of strychnine spikes was found to increase under the influence of acetylcholine and this effect was reversible. Finally, it was shown that the excitatory effect of small doses of intravenously injected acetylcholine on the cortex was greatly reduced or abolished in the ipsilateral cortex after unilateral lesions in the posterior hypothalamus.[1] From these data it is concluded that baroreceptor impulses influence cortical activity via the hypothalamic-cortical system. These conclusions are in agreement with the work of Bonvallet, Dell and Hiebel (1954).

The fact that relatively small variations in the blood pressure cause distinct changes in the cortical potentials and in their frequency pattern suggest that the sino-aortic receptors exert a homeostatic effect on the cerebral cortex. As the pressure in the carotid sinus falls the discharges of the baroreceptors which restrain hypothalamic and indirectly cortical activity are diminished; the hypothalamic activity and indirectly (through the hypothalamic-cortical discharge) the cortical activity increase and thereby counteract the effects of a fall of the blood pressure. When the pressure in the carotid sinus increases the opposite effects take place. This view is somewhat opposed to the experimental results of Porter (1952) and Bonvallet *et al.* (1954), who stress the excitatory action of adrenaline on the hypothalamus and the reticular system although the French authors emphasize the restraining influence on the cerebral cortex of a marked increase in intrasinusal pressure. On the basis of our experience, it is believed that the excitatory effects of adrenaline occur mainly with relatively large doses of adrenaline or nor-adrenaline and that within physiological limits the homeostatic role of these neurohumors prevails.[2]

It was previously shown in this laboratory (Redgate and Gellhorn 1955; Gellhorn and Redgate 1955) that hypotensive drugs (acetylcholine, mecholyl, and histamine) lead, as the blood pressure returns to the control level, to a sympathetic discharge the intensity of which is related directly to the excitability of the posterior hypothalamus. There seems to be a parallelism between the autonomic changes evoked by hypotensive drugs and the action on the cerebral cortex. Apparently, hypotensive drugs cause an excitation of this structure which results in an increased cortical (upward-) and an autonomic (downward-) discharge. Hypertensive drugs seem to diminish these discharges. This effect involves the posterior hypothalamus indirectly. According to Gellhorn, Nakao and Redgate (1956) hypertensive drugs lead to increased parasympathetic discharges from the anterior hypothalamus while the excitability of the posterior hypothalamus is reciprocally diminished. These investigations confirm and extend the previous work on the action of carbon dioxide and barbiturates on the hypothalamus (Gellhorn 1953) in which it was shown that alterations in the excitability of the posterior hypothalamus lead to parallel

[1] Unpublished work.

[2] This is in agreement with the work of Lundberg (1952) and Celander (1954).

changes of the upward- (cortical) and downward- (sympathetic) discharges from the hypothalamus.

The clinical implications of this work are discussed elsewhere (Gellhorn 1956).

## SUMMARY

On the basis of EEG records and EEG analysis by means of an Offner analyser the following results have been obtained in cats on the role of the sino-aortic baroreceptors for the action of hypo- and hypertensive drugs:

1. Adrenaline and nor-adrenaline induce the appearance of grouped (''Dial'') potentials during the hypertensive phase. This effect is reversibly abolished by small amounts of barbiturates. On analysis this action of adrenaline and nor-adrenaline is found to be associated with an increase in the slow potentials and often also with a decrease of the fast potentials in the EEG. After sino-aortic denervation this action of the two hypertensive drugs is abolished or reversed.

2. Hypotensive drugs such as acetylcholine cause a cortical excitation characterized by an increase in the amplitude of the fast potentials and often also by a simultaneous decrease in the amplitude of the slow potentials. This action of acetylcholine is greatly reduced or abolished by sino-aortic denervation.

3. From these experiments it is inferred that baroreceptor reflexes exert a homeostatic influence on the activity of the cerebral cortex.

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# EFFECT OF DRUGS ON PYRAMIDAL DISCHARGES EVOKED BY CORTICAL STIMULATION [1]

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Since the recognition of the role of cholinergic and adrenergic compounds in neuromuscular and neuroglandular transmission, the effects of such drugs on transmission in the central nervous system have been studied frequently. In these studies there is implicit acceptance of Feldberg's opinion (Feldberg and Vogt 1948), based on regional enzymatic distribution, that the pharmacological sensitivity of neurons varies from tract to tract and from stage to stage in the same tract. There is some evidence that cholinergic drugs affect the motor systems at the upper level. Fiamberti (1937) produced convulsions in man by intracisternal injection of acetylcholine. Miller (1938), Moruzzi (1939), Williams (1941), McKail, Obrador and Wilson (1941), and Forster (1945), although employing different techniques, all concluded that administration of cholinergic drugs increases activity of the motor systems.

None of these studies, however, localizes the site at which the drugs act. In the present experiments cholinergic and adrenergic drugs have been studied as they affect the electrical response of the pyramidal tract to cortical stimulation. As Patton and Amassian (1954) have shown, the cortically evoked pyramidal response consists of an early D wave, due to direct excitation of pyramidal cells, followed by a series of I waves, due to re-excitation of pyramidal cells through cortical interneurons. Thus, the excitability of pyramidal units and cortical interneurons can be studied separately. The validity of this technique has recently been confirmed by Zanchetti and Brookhart (1955).

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[2] Fulbright grantee 1953-1954. Now at Institut de Thérapeutique expérimentale, Liège, Belgium.

## METHODS

The experimental animals were 26 cats and 4 monkeys anesthetized with Dial (0.6 ml/kg., intraperitoneally) or Nembutal (0.4-0.6 ml/kg., intraperitoneally). Sometimes the animal was immobilized with decamethonium bromide; artificial respiration was used in these instances.

Single shocks (45/min.) were delivered to the motor cortex through bipolar electrodes. Pyramidal discharges were recorded on a cathode ray oscilloscope, sometimes supplemented by an inkwriter. The recording electrodes were single nichrome wires, with a bare tip diameter of about 40 $\mu$, inserted into the lateral spinal column at $C_1$. A detailed description of the technique and analysis appears in Patton and Amassian's report (1954).

Cholinergic and anticholinergic drugs were injected, intravenously or intracarotidly, or were applied topically to the cortex on 2 mm. squares of filter paper. In the cats, the internal carotid was often atrophic (Davis and Story 1943) or very fine. However, since the external carotid contributes an important part of the cerebral blood supply, the injection was made via the common carotid. To reduce dispersion of injected solutions, the lingual artery was tied, and the carotid sinus was denervated to eliminate indirect effects.

The injections were usually given at a rate of 0.5 ml. in 5-10 sec. Numerous tests indicated that saline injections given at this rate did not affect pyramidal responses.

## RESULTS

*Interpretation of records.* The effects of the injected drugs were assayed by measuring the latencies and amplitudes of both the D and the I waves before and after drug administration. The latencies of all components

proved to be independent of drug action; significant alterations were reflected only in amplitude changes. Because the discharge (particularly the I waves) is asynchronous and also because the responses from injured and uninjured fibers are unavoidably mixed (Patton and Amassian 1954), amplitude measures only roughly indicate the size of the active cortical pool. While measurement of the area rather than the amplitude of waves diminishes errors resulting from asynchrony, the waves (particularly I waves) in pyramidal discharges often overlap so that the establishment of boundaries for area measurements is somewhat arbitrary. In experiments in which the waves were sufficiently discrete, measured areas correlated well with amplitude measurements. Therefore, we have routinely measured only amplitudes.

*Intracarotid injections of acetylcholine.* Intracarotid injections of acetylcholine caused characteristic and reproducible changes in the amplitude of the corticospinal discharges. These changes were for the most part confined to the I waves (fig. 1); D waves decreased in amplitude only when very large doses were given or when the rate of injection was rapid. With moderate doses (5-20 $\mu$g, injected at a rate of 0.5 ml. in 5-10 sec.) the D waves were unaffected. With this dose the I waves, however, underwent an initial increase in amplitude, which began a few seconds after injection, followed by a prolonged period in which the amplitude of the I waves was markedly

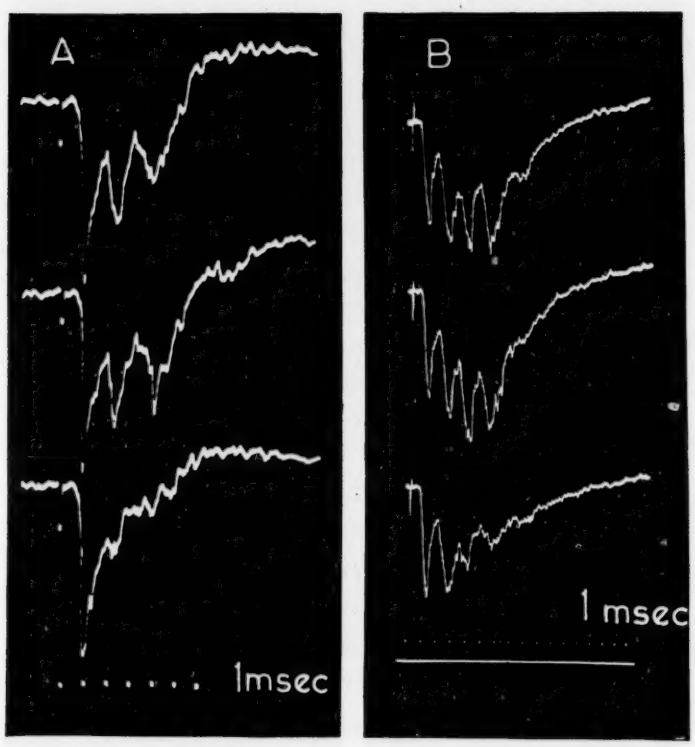


Fig. 1

Pyramidal responses to cortical stimulation. A: cat, Dial anesthesia. B: monkey, pentobarbital anesthesia. Upper, control trace. Middle, 10 sec. after intracarotid injection of 10 $\mu$g. of acetylcholine. Lower, 1 min. later during depression of I waves. Positivity downward. Time: 1 msec.

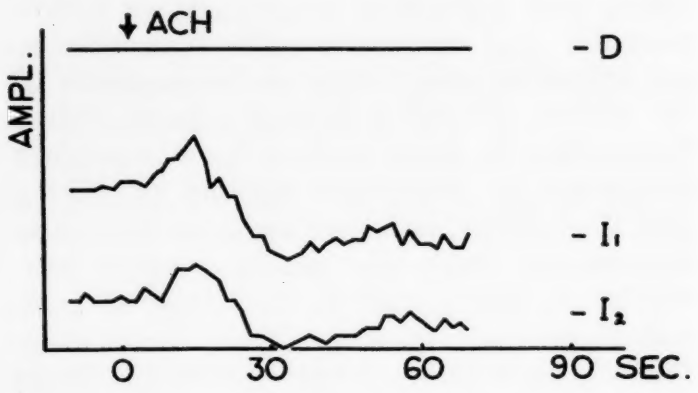


Fig. 2

Effect of eserine and acetylcholine on the components of cortically evoked pyramidal discharges. Cat, Dial anesthesia. Arrow indicates intracarotid injection of 5 $\mu$g. of acetylcholine (1 min. after injection of 250 $\mu$g. of eserine). Eserine alone had no effect on pyramidal discharges. Time in seconds. Measured amplitudes in arbitrary units.

diminished (fig. 2 and 3). Interestingly, the second I wave and, in monkey, the third and fourth varied more pronouncedly than the first. In extreme instances the late I waves were completely abolished. The independent

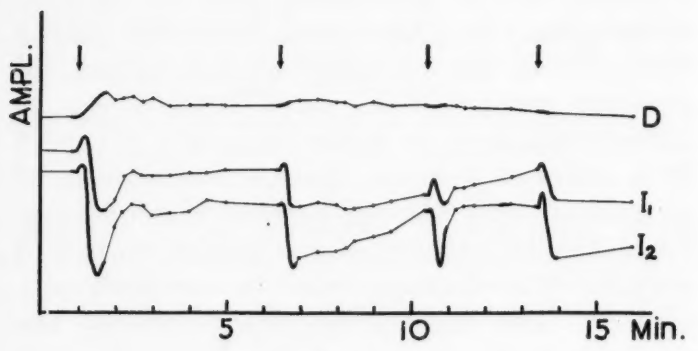


Fig. 3

Effect of repeated injections of acetylcholine on pyramidal discharges. Cat under Dial. Arrows indicate intracarotid injections of 5 $\mu$g. of acetylcholine. Heavy lines indicate periods during which measurements were made on successive records taken at the rate of 45/min. Other records and measurements were less frequent, each being represented by a dot. Time in minutes. Amplitude in arbitrary units.

behavior of I waves suggests that different interneurons are responsible for their production, and hence can be separately influenced.

The initial phase of augmentation usually lasted 20-30 sec. (45 sec. in one monkey). During this period the first I wave might attain 125 per cent and the second I wave 140 per cent of the respective control amplitudes.

The later phase of depression varied from 1-15 min., and as mentioned above, was occasionally so marked that I waves disappeared completely.

These effects of acetylcholine were enhanced by antecedent administration of eserine. Ineffective quantities of acetylcholine could be made effective by previous eserine dosage. In figure 2 is shown an instance in which 5 $\mu$g. of acetylcholine were effective only when they followed an injection of 250 $\mu$g. of eserine.

Atropine administered alone did not affect pyramidal discharges, but prevented the action of acetylcholine given in amounts which were quite active when administered alone.

*Intracarotid injections of other drugs.* Several other drugs duplicated the action of acetylcholine on pyramidal discharges. These included: eserine (200-400 $\mu$g), mecholyl (0.2-5.0 $\mu$g.), d-tubocurarine (100-200 $\mu$g.), histamine (1 $\mu$g.), and nicotinic acid (4 $\mu$g.). The effects of these drugs were indistinguishable from those of acetylcholine.

*Other routes of administration.* Eserine, administered *intravenously,* depressed I waves, although the effective doses (0.5-1 $\mu$g.) were larger than those active intracarotidly and the early phase of augmentation was lacking. *Topical applications* of drugs to the cortical surface were almost uniformly without effect on cortical excitability as measured by pyramidal discharge. The test substances included: acetylcholine (2-10 per cent), mecholyl (1-2 per cent), eserine (1-10 per cent), and DFP (1.84 per cent). The filter papers saturated with the drugs were left in place for 3-15 min., and were removed before the stimulating electrodes were applied for testing. Rarely, such treatment caused slight depression of both D and I waves, but usually, the results were entirely negative. Careful observation of pial vessels revealed no change in their size following topical application of drugs.

*Inhalation* of amyl nitrite duplicated almost exactly the effects of intravenous eserine on pyramidal discharges.

## DISCUSSION

Our results indicate that intracarotid injection of acetylcholine causes predictable changes in the excitability of cortical cells. The effects are due to specific action of the drug, and are enhanced by eserine and abolished by atropine. There is reason to believe, however, that the drugs do not act directly on the cortical cells but rather affect their excitability secondarily, through vascular changes.

Topical application of acetylcholine, and other drugs effective by the intracarotid route, to the motor cortex was ineffective. Zanchetti and Brookhart (1955) similarly found Metrazol and pentobarbital ineffective when topically applied. Baruk *et al.* (1948) showed that pial vasodilatation occurs when acetylcholine is administered intravascularly but not when it is topically applied to the cortex.

Moreover, the effects of acetylcholine on cortical excitability were reproduced by several drugs with very different natures but having the common property of producing vascular changes. These included: eserine, mecholyl, d-tubocurarine, histamine, nicotinic acid, and amyl nitrite (by inhalation). For most of these agents a cerebral vasodilator function is well established (Wolff 1936). For nicotinic acid, vasodilatation was noted by Aring *et al.* (1941) and by Huertas and Foster (1954). It therefore seems likely that the observed effects were largely secondary to the vascular changes.

These findings emphasize the importance of interpreting cautiously experiments in which effects of so-called neurohumoral agents on the central nervous system are studied. For example, the effect of d-tubocurarine on electrical activity in the dog's brain reported by McIntyre (1946) was similar to that reported here and hence is susceptible to an explanation involving vascular mechanisms. Similarly, it may be suggested that

the "permissive" effect of atropine on the augmentation of primary evoked cortical potentials induced by acetylcholine may result from exclusion of vascular concomitants rather than from inactivation of an atropine-sensitive inhibitory mechanism, as suggested by Chatfield and Purpura (1954).

Vascular origin of acetylcholine's effects on cortical excitability would also account for the great variability of these effects (Chatfield and Purpura 1954; Essig *et al.* 1953; Chusid *et al.* 1952), for it is well known that the vascular action of cholinergic drugs is conditioned by the previous state of the vessels. The arguments of Forster *et al.* (1946) against a vascular origin of cortical depression following acetylcholine were based on recordings of systemic blood pressure and do not take into account the possibility of local changes in cortical circulation. Leão (1944) has shown that such local vascular changes are closely related to cortical excitability.

An interesting conclusion from our studies is that eserine- or acetylcholine-induced convulsions are not caused by direct action of these drugs on the corticospinal tract. We frequently observed violent spontaneous pyramidal activity following drug treatment at a time when the evoked response was either unaltered or even diminished. Zanchetti and Brookhart (1955) similarly observed no change in pyramidal responsiveness when Metrazol had been administered in doses large enough to induce "spontaneous convulsive discharges". These observations suggest that the convulsive activity must originate elsewhere than in the pyramidal neurons and the cortical interneurons responsible for I waves. It may be that convulsants act partly by opening communications between incoming afferent systems and the pyramidal cells (Chatfield and Purpura 1954).

## SUMMARY AND CONCLUSION

1. The effects exerted by various drugs on pyramidal discharges evoked by cortical stimulation were studied in cats and monkeys.

2. Intracarotid injection of acetylcholine caused a brief period of augmentation followed by a prolonged period of depression in pyramidal discharges. Discharges (I waves) depending on cortical interneuronal bombardment of pyramidal cells were the most prominently affected.

3. The effects of acetylcholine were augmented by eserine and blocked by atropine.

4. Injections of eserine, mecholyl, d-tubocurarine, histamine and nicotinic acid, and inhalation of amyl nitrite affected pyramidal discharges in the same way as acetylcholine.

5. It is concluded that the effects of these drugs are attributable to cortical vasodilatation.

6. Because the pyramidal neurons and the cortical interneurons which reactivate them are not directly affected, it is concluded that motor effects induced by cholinergic drugs originate elsewhere.

I am deeply indebted to Drs. V. E. Amassian, H. D. Patton and T. C. Ruch for their kind support and invaluable help during this investigation. Especially I wish to thank Dr. H. D. Patton for his friendly criticism in interpreting and writing these observations.

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*Reference*: SCHLAG, J. D. A. Effect of drugs on pyramidal discharges evoked by cortical stimulation. *EEG Clin. Neurophysiol.*, **1956**, *8*: 421-425.

# *ANNOUNCEMENT*

## FIRST INTERNATIONAL CONGRESS OF NEUROLOGICAL SCIENCES

### BRUSSELS 1957

### Preliminary announcement

Having regard to the decision of the General Assembly of the International Federation of EEG Societies at the close of its Third Congress in Boston, the Organizing Committee of the Fourth International Congress has decided to held its sessions, jointly with the International Congress of Neurology, in 1957 in Brussels, *from the 21st to the 28th of July.*

The overall designation of the Congress will be as follows: ''First International Congress of Neurological Sciences'' sub-titles: Sixth International Congress of Neurology, Fourth International Congress of Electroencephalography and Clinical Neurophysiology, Third International Congress of Neuropathology, First International Congress of Neurosurgery, Fifth Meeting of the International League Against Epilepsy and Fifth Symposium Neuroradiologicum.

***Congress Organising Committee :***

President : F. BREMER.

***Ex-officio members :***

Officers of the International Federation of Societies for Electroencephalography and Clinical Neurophysiology.

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| W. GREY WALTER, | President |
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| J. TITECA, | Treasurer General |
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The whole Congress will take up the six working days of a week. On the Sunday before the Congress, during the morning, there will be the meeting of the International League Against Epilepsy and in the afternoon the Plenary Opening Session of the Congress, with a formal reception in the evening. The morning of the Sunday following the Congress will be given up to private administrative meetings of the various disciplines which are to be united in the Congress. These meetings will be followed by a general meeting of all delegates, which will take decisions, according to the experience acquired during the Congress and the wishes of the various groups, on the form and organization of future International Congresses.

The time allocated to each discipline will be strictly equitable, as far as possible, for their participation in the general themes accepted by the majority of committee members for the two common days.

These are :

1. The pathology of the extra-pyramidal system.
2. The significance and interpretation of alterations in Consciousness.

***Chosen themes (EEG) for the other four days***

1. The interpretation of normal and pathological muscle potentials.
   (*a*) Parameters and patterns of the motor unit.
   (*b*) The physiopathology of central mechanisms.
   (*c*) The physiopathology of neuro-muscular mechanisms.
2. The EEG in conditioned behaviour.
3. Electroencephalographic ''abnormalities'' as signs of brain pathology.
4. Symposium on the pathogenesis and clinical aspects of ''Petit Mal'' epilepsy.
5. Symposium on the ontogeny of the EEG.

Since it has been decided to arrange for complete publication and *precirculation* of the Reports and Free Communications, it is necessary that these be sent to the Organizing Committee of the Congress *at the latest by 1st February, 1957.* A Free Communication will definitely not be accepted unless the author has remitted his subscription to the Congress. In order to make sure that the meetings go smoothly, with the most extensive audience and discussion, the Committee strongly urges that the National Societies should themselves exercise some selection of communications. Each participant has the right to a single Free Communication, which may be signed by the author alone or with collaborators. The Organizing Committee will work out the most effective means of arranging the Free Communications so as to provide the greatest possible immediate interest for the majority of the audience. These means will be described in more detail in subsequent communications.

The subscription rate for the whole International Congress of Neurological Sciences will be $15.00 for each participant who is a registered member of one of our Federated Societies, $10.00 for associate members, i.e. physicians or scientists interested in Neurology, and $5.00 for subscribing members, that is unqualified persons who are interested in the subjects of the Congress. As in the case of the National Societies of Neurology, Neurosurgery and Neuropathology, the various national EEG Societies will be expected to contribute to the organizing expenses of the Congress. The Neurological and Neurosurgical Societies have accepted the principle of a pro rata contribution of $1.00 per member per year from 1955 to 1957, *that is $2.00 per affiliated member.* In any case where this raises practical difficulties, we are sure that our national EEG Societies will be able to make a financial contribution in proportion to their means and membership. Intention to participate at the closing Banquet will have to be indicated at the time of subscription to the Congress and the separate subscription to this function will have to be remitted with the general subscription.

The Reports and Free Communications will be published in French or in English. The principle of equality of language has been accepted for the oral delivery of communications. Nevertheless, if the greatest possible number of listeners is to understand the communications, it will be necessary to reduce to some extent the number of languages to be spoken. At the present time, the Organizing Committee envisages the possibility of simultaneous translation for English, French and German. For communications in other languages, the author is asked to send in a translation of his paper in one of the three official languages (French, English and German) in triplicate to facilitate simultaneous translation.

The official travel Agencies for the Congress are: The American Express Company and Thomas Cook & Son.

# THE RELATION BETWEEN ELECTRO-CORTICAL WAVES AND RESPONSIVENESS OF THE CORTICO-SPINAL SYSTEM [1]

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## INTRODUCTION

Many years have elapsed since the first description of electrical changes at the cerebral cortex occurring spontaneously (Berger 1930) or following diencephalic stimulation (Morison and Dempsey 1941: Dempsey and Morison 1942a; Dempsey and Morison 1942b). During this time relatively little has been learned about the significance of these changes or about their influence on the behavior of cortical neuron systems. It was considered possible that some insight into the significance of these electrical variations might be forthcoming in the light of information relating cortical potentials and excitability changes in a corticifugal system.

As a means of attacking this problem, we have elected to determine what changes in cortical responsiveness occur coincidentally with the development of three different forms of repetitive cortical electrical activity which may be produced experimentally in a controlled fashion. Cortical potential changes in the sensori-motor cortex may be evoked by single shock or repetitive stimulation of the specific relay nuclei — ventralis lateralis, ventralis postero-lateralis and ventralis postero-medialis. Single shocks to the nuclei are followed by a diphasic change of cortical potential. Low frequency, 7-12/sec., stimulation of the same site will result in the appearance of a larger potential fluctuation with a slightly different time course than that following a single shock — the augmenting response (Dempsey and Morison 1942a). Cortical potential changes have also been evoked by repetitive stimulation of one or more of the diffusely projecting thalamic nuclei, thus producing recruiting responses at the cerebral cortex (Dempsey and Morison 1942b). During the past few years a great deal of effort has been expended in an analysis of the components of this system (Starzl and Whitlock 1952; Verzeano, Lindsley and Magoun 1953; Hanbery and Jasper 1953; Hanbery, Ajmone-Marsan and Dilworth 1954; Arduini and Terzuolo 1951; Arduini and Whitlock 1953), but the significance of these cortical waves in terms of the functional changes which they induce still remain obscure. We have also utilized the spontaneous spindle burst (Derbyshire, Rempel, Forbes and Lambert 1936; Bremer 1935; Bremer 1938) which is so familiar to all who have recorded cortical electrical activity during sleep, barbiturate narcosis or coma of other sorts.

All three of these forms of electro-cortical activity have certain features in common. They may all be recorded from the sensori-motor cortex of the cat. They may all be produced by the arrival of a synchronized volley in efferents to the cerebral cortex from sub-cortical structures. They all involve potential fluctuations of the same order of magnitude (250-1000 $\mu$V.). They all have a similar time-course involving an initial surface positivity (minimal and sometimes lacking in the recruitment responses), a subsequent surface negative wave of considerable amplitude and duration, and a variable degree of terminal surface positivity. And finally, they all seem to involve rhythmic activity in systems which operate most effectively at frequencies similar to that of the normal alpha rhythm (7-12/sec.). In consideration of these similarities, one might be

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justified in predicting that the intracortical events accompanying these changes in surface potential might also be similar in all three cases.

We have attempted to test this prediction by studying the responsiveness of the cortical system giving rise to cortico-spinal axones during these three forms of cortical potential change. The response evoked in cortico-spinal axones by electrical stimulation of their cells of origin in the motor cortex has been described and analyzed by Patton and Amasssian (1954). The alterations in this response have been examined during procedures which are known to depress or enhance neuronal excitability. It has been concluded that the cortically evoked pyramidal volley may be used as a measure of the responsiveness of the cells of origin of these fibers and of the cortical neurones directly related thereto (Zanchetti and Brookhart 1955).

The study reported here demonstrates that when the cerebral cortex is conditioned by repetitive activity evoked in the specific thalamic relay nuclei, or by activity accompanying spontaneous spindle waves, clear-cut alterations in the responsiveness of this cortical efferent system may be detected. When the cortex is conditioned by low frequency stimulation of the mid-line portions of the diffuse thalamic projection system, no alterations in responsiveness of this efferent system are detectable. Despite the similarity of the electrical changes occurring at the cortical surface, the results indicate the existence of at least two totally different mechanisms for the production of these electrical changes.

## METHODS

The results to be reported have been drawn from studies carried out on 33 cats. Under ether anesthesia, the trachea was cannulated, the head mounted in a stereotaxic frame and the cranial vault exposed. Small trephine holes were made to permit the introduction of coagulating electrodes, diencephalic stimulating electrodes and pyramidal recording electrodes. The sensori-motor cortex was exposed through the frontal sinus. Cortical stimulating electrodes, consisting of spring-mounted ball-tipped silver wires separated 3-4 mm., were placed extradurally by direct vision. Extradural stimulation was used almost exclusively, since it was felt that the almost insignificant increase in threshold to electrical stimulation was more than offset by the stability of the cortex resulting from its protection by the dura. Intracranial electrodes were placed stereotaxically. Diencephalic stimulating electrodes were concentrically bipolar with a tip separation of approximately 0.5 mm. The pyramidal response was derived from similar electrodes with a greater tip separation. Following the surgical preparation of the animal and the placement of the electrodes, the infra-orbital, supra-orbital and auricular nerves and the edges of the scalp were infiltrated with procaine. In the experiments involving stimulation of the specific thalamic nuclei or the diffusely projecting thalamic nuclei, the animals were immobilized with decamethonium bromide and were maintained on continuous artificial ventilation.[1]

Decamethonium bromide was administered at a dose level of 1 mg. repeated every 45 to 60 min. and ether was discontinued. The subsequent search for a suitable site for diencephalic stimulation occupied sufficient time to permit the major effects of the ether to be dissipated. In the experiments requiring spontaneous spindle bursts, the animals were subjected to a partial lesion of the mesencephalic reticular formation. This was accomplished through the use of thermocoagulation produced by radio-frequency currents in such a way as to spare the basis pedunculi on the side stimulated (Whitlock, Arduini and Moruzzi 1953).

Stimulating pulses were in all cases rectangular pulses slightly distorted by an isolating transformer. Cortical pulses were 0.15 or 0.2 msec. in duration with a peak current of 0.75-1.5 mA. delivered at intervals of not less than 2 sec. The threshold and sensitivity of the cortical efferent system was routinely tested and recorded at the initiation of each experiment and usually several times during

[1] Syncurine was furnished through the generosity of the Burroughs Wellcome Co. and was used in order to avoid alterations of cortical function which may accompany the use of curare-like compounds (Chang 1953).

the experiment. A stimulus intensity was chosen which fell on the steepest portion of the intensity-response curve, thus affording the greatest opportunity for detecting either an increase or decrease of responsiveness.[1]

Diencephalic pulses varied between 0.1 and 1.0 msec. in duration depending upon the type of activity being evoked. Intensity was adjusted to a value adequate to produce reliable and reproducible cortical responses (2-5 V.). Optimum frequencies for the responses under consideration varied from animal to animal through the range of 7-12/sec. Train duration for diencephalic stimuli was held constant during each experiment through the operation of an electronic gate. Suitably interrelated delay circuits permitted the proper timing of the testing cortical pulse and the recording oscilloscope sweep.

Two recording systems were generally employed during each experiment. The optimal point for diencephalic stimulation was determined by observing the evoked cortical responses on a multi-channel electroencephalograph (Grass Model IIID). The best position for the diencephalic electrode having been determined, recordings were then made photographically from a dual-channel oscilloscope driven by a pair of matched, differentiating preamplifiers (Tektronix Type 122). The pyramidal response was taken from the mid-olivary portion of the medullary pyramid. The conditioning cortical activity was usually recorded from a monopolar electrode midway between the stimulating electrodes on the sensori-motor cortex, the reference leading from the edge of the scalp.

Due to the presence, in most animals, of minor uncontrollable fluctuations in responsiveness of the pyramidal efferent system, a routine of recording was devised which made possible the application of small-sample statistical methods to the treatment of the data. The cortical response to diencephalic stimulation was first recorded on a short strip of moving film. The film strips provided evidence of the time course and stability of evoked cortical response and at the same time provided the means for measuring the time interval between the conditioning and testing stimuli. Following this, 10 superimposed records of the pyramidal response conditioned by diencephalic stimulation were recorded with a moving sweep on stationary film, intervals of 20-40 sec. being allowed to pass between bursts of diencephalic stimulation. On the adjacent frame, 10 superimposed traces of the unconditioned pyramidal responses were then recorded. Response areas were measured planimetrically in the manner described previously (Zanchetti and Brookhart 1955). In most experiments a recording of the baseline was often made on the same frame with the superimposed pyramidal responses to increase the accuracy of the area measurement.

Since the D and I portions of the complex are expressions of activity in different neurone groups, it seemed worthwhile to examine the changes in D and I response areas separately. This has been done with full knowledge of the probability that such a separation of response areas cannot be accurately achieved since the trailing edge of the D wave overlaps the beginning of the first I wave.

The inability to control the timing and duration of spontaneous spindle bursts necessitated modification of this recording routine. In these experiments, advantage was taken of the fact that, in preparations with an adequately responsive cortex, the individual spindle waves are accompanied by discharges over the cortico-spinal fibers (Whitlock, Arduini and Moruzzi 1953). Since these spontaneous discharges as well as the evoked pyramidal response could be recorded from the pyramidal electrode, the spontaneous pyramidal discharge was utilized to activate a monitoring oscilloscope. The monitor (Tektronix Type 512) was adjusted for internal triggering in such a way that its slow-moving sweep began its traverse only when the pyramidal discharges reached an adequate amplitude. The cortical testing pulse was delayed

[1] Throughout this presentation we have attempted to use the words *threshold* and *excitability* with reference only to the relationship between liminal stimulation and minimum response; the word *sensitivity* with reference only to the slope of the intensity-response curve; and the word *responsiveness* in a more general way where specific reference to either excitability or sensitivity seemed undesirable.

on the monitor sweep saw-tooth, the whole arrangement resulting in an automatic triggering of the cortical pulse shortly after the pyramidal spindle discharges were well developed. The pyramidal discharges just preceding the cortical shock were recorded with a relatively slow sweep from one tube of the dual oscilloscope at the same time that the evoked was recorded with a fast sweep on the other tube. Since the individual spindle discharges were somewhat variable in contour and temporal characteristics, it was impossible to superimpose records of evoked pyramidal responses initiated during the same phase of the pyramidal spindle discharge. Consequently, numerous evoked pyramidal volleys were recorded on individual frames. With the aid of a photographic enlarger, single responses initiated during similar phases of the pyramidal discharge were then copied as superimposed tracings and quantitative data were derived from these copies.

At the termination of the experiment, the head of the animal was perfused through one carotid artery with 10 per cent formalin in physiological saline. The diencephalic and pyramidal electrodes were left *in situ* overnight while the brain hardened. The vertical stereotaxic planes were then marked by inserting electrodes at appropriate levels while they were wet with India ink. The brain was removed, blocked, frozen and sectioned at 100 microns. Alternate sections through areas of electrode tracks or coagulation were stained by the Weil technique and with carbol-thionin. Electrode positions were determined from the sections.

## RESULTS

Specific Thalamic Nuclei: *Single Evoked Response.* In a group of four experiments single shocks were delivered to the thalamus at foci which gave rise to evoked cortical responses in the region of the stimulating electrodes near the cruciate sulcus. Stimulation of ventralis postero-lateralis, ventralis postero-medialis, or ventralis lateralis produced a short latency, initially positive diphasic response at the cortical surface. The cortical responses were accompanied in 2 of these animals by a pyramidal volley which began approximately 2.0-3.0 msec. after the thalamic pulse and endured for 2-3 msec. through the initial portions of the positive phase of the cortical response. This pyramidal volley evoked by thalamic stimulation was not dependent upon spread of excitation to fibers of the internal capsule and is therefore to be referred to as the *relayed response.* No relayed response appeared in 2 of these animals. In these 2 animals it was impossible to detect any alteration of the responsiveness of the efferent system during or following the cortical response to thalamic excitation. In the 2 animals in which small relayed responses appeared there was a suggestion of prolongation of the conditioned I wave during the late positive and subsequent negative phases of the cortical response. However, the range of variation of both unconditioned and conditioned I waves was of such an order as to make it doubtful that this was a significant change in the response area of the I wave.

Specific Thalamic Nuclei: *Repetitive Stimulation.* When VPL, VPM, or VL was stimulated repetitively at frequencies of 7-10/sec., the evoked cortical response changed during the first few stimuli. This phenomenon was first noted by Dempsey and Morison (1942a) who introduced the term *augmenting response* and suggested that the changes were due to the activation of an additional, distinct thalamo-cortical process. In the unanesthetized cortex, the development of the augmenting response occurred in a manner quite similar to that described for the anesthetized cortex. This is illustrated in the tracings presented in figure 1. The most prominent of the changes observed were (*a*) the increase in amplitude and time-to-peak of the initial positive component; (*b*) the appearance of a second period of pronounced negativity which augmented in amplitude and duration with each stimulus; and (*c*) the development of a second positivity following the negative wave. We have made no careful observations on the distribution of the augmenting response as compared to the response to a single stimulus, but our EEG recordings indicate that elements of this response may be detected over cortical areas bordering on the posterior sigmoid gyrus.

Concurrently with the growth of the augmenting response, there occurred a growth in the amplitude and duration of the relayed pyramidal volley. The changes in the relayed volley which were typical of these experiments

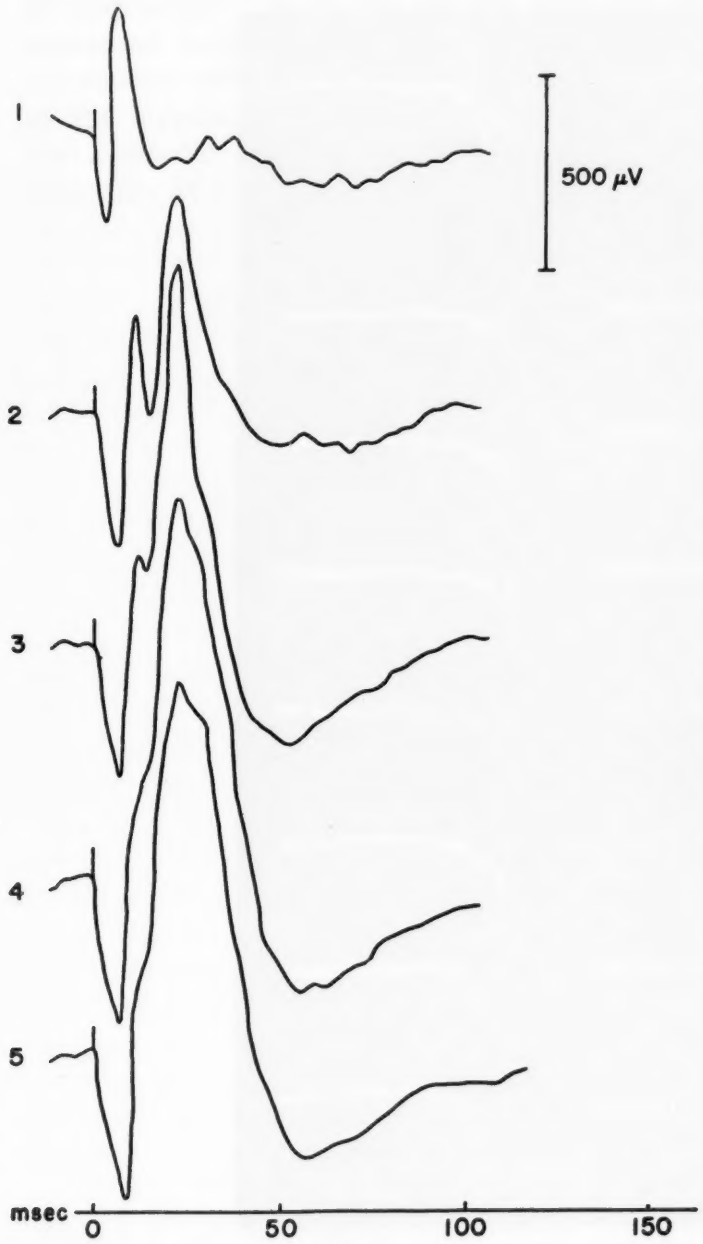


Fig. 1

Tracings of a sequence of 5 augmenting responses oscillographically recorded from the anterior sigmoid gyrus during stimulation of the n. ventralis posterolateralis. Pulse 1.0 msec. at 8 per sec. (1-29-54).

are illustrated in the lower trace of figure 2 (top), although its separation into two components was not always so clearly evident as in these particular records. The initial portions of the relayed volley were clearly related both in time and magnitude to the surface positive phase of the cortical response. The later portion of the relayed volley was related to the development of the negative deflection of the augmenting response mentioned above. In consideration of the timing and lability of the latter portion of the relayed volley, it seems impossible to assign it to pyramidal fibers of slower conduction velocity (Bishop, Jeremy and Lance 1953).

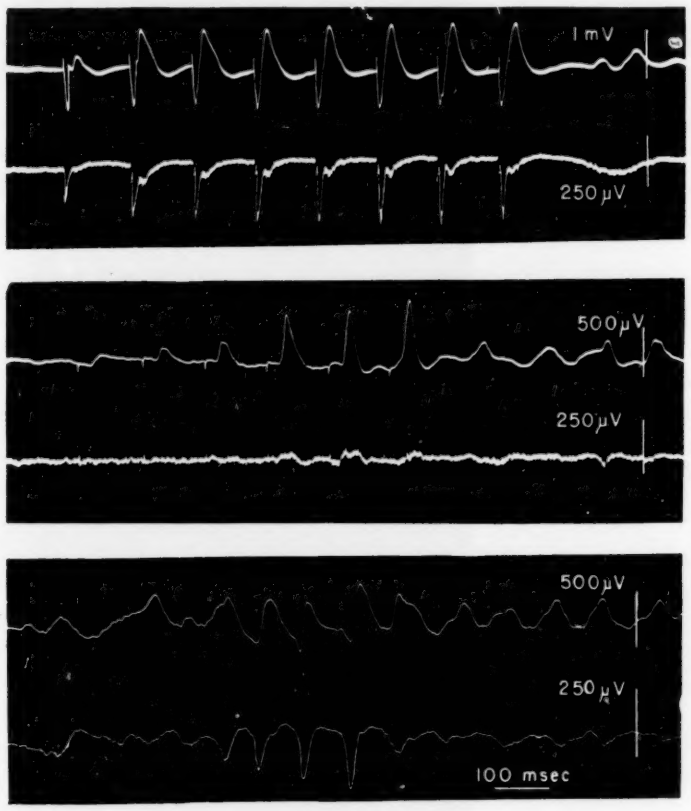


Fig. 2

Simultaneous recordings from the anterior sigmoid gyrus (upper trace) and medullary pyramid (lower trace). Top: unanesthetized cat. Augmenting responses initiated by stimulation of n. ventralis lateralis. Note the "relayed" pyramidal volleys.

Middle: similar recordings from another preparation. Recruiting response initiated by stimulation of n. reuniens. Note the stability of the pyramidal recording.

Bottom: recordings taken during spontaneous spindle burst in an unanesthetized cat with mesencephalic thermocoagulation. Note the relayed spindle waves in the pyramidal recording. In this experiment the frequency response of the preamplifier was altered to eliminate higher frequency components.

The responsiveness of the pyramidal efferent system was tested during the various phases of the augmenting response after it had undergone complete development through 3 to 6 antecedent thalamic stimuli. The observations on 11 cats have been consistent qualitatively and have shown only minor quantitative variations. The basic data from

such experiment are illustrated in figure 3. The figure is arranged so that samples of the unconditioned response taken during various portions of the experiment are placed for comparison on the top row. In columns below are shown responses recorded at the various indicated times before and after the fifth and last thalamic stimulus. From — 10 to + 3.0 msec. the pyramidal efferent system was in a state of diminished responsiveness which was sufficiently severe to abolish all but a small portion of the evoked D wave. In fact, the record taken at + 3.0 msec. shows primarily the relayed volley following the thalamic stimulation artifact. Three milliseconds later, the responsiveness of the pyramidal efferent system had suddenly shifted. The evoked response was recorded on the tail of the relayed volley and indicates an enhancement of responsiveness at that time. Even though the response areas of the D and first I wave were not obviously greater than

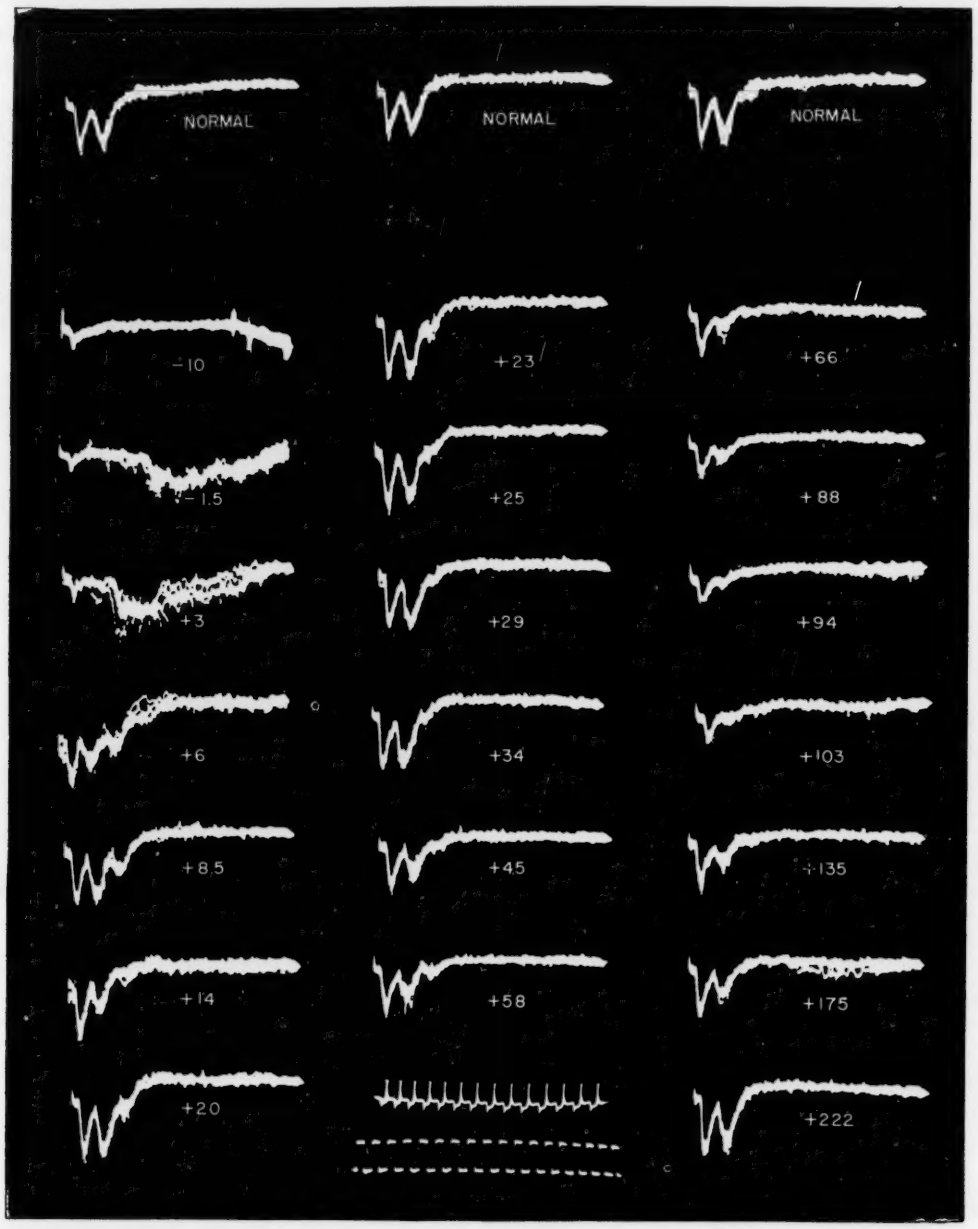


Fig. 3

Unanesthetized cat. Pyramidal volleys evoked by stimulation of anterior sigmoid gyrus (0.2 msec. 1.75 ma.). Normal responses at top of figure. Cortex conditioned by augmenting waves initiated by stimulation of n. ventralis postero-lateralis (1.0 msec. at 8 per sec.). Testing shocks delivered at indicated times before (—) and after (+) the fifth and last thalamic stimulus. Each record consists of 10 superimposed responses. Calibrations: 1 msec., 100 $\mu$V. (1-29-54).

those of the unconditioned response, the record is altered by the appearance of a second I wave. For reasons which will appear obvious after examination of figures to be presented later, we have come to regard the appearance of additional I waves as certain evidence of increased responsiveness on the part of the pyramidal efferent system. This facilitation of the pyramidal efferent system continued for some 25 msec. after the last thalamic stimulus. It was supplanted, at approximately 45 msec., by the beginning of a period of depression. During the next 40 msec. the depression continued to grow more severe, reaching its maximum in the record taken at 103 msec.

At this time, the response area of the I wave was almost zero, and the response area of the D wave had been severely reduced. The period of depression lasted until 175 msec. after the last thalamic stimulus. The record taken at 222 msec. showed a slight increase in response area coincident with the development of a repetitive (Morison, Dempsey and Morison 1941) or reverberating wave (Chang 1950). In the majority of our experiments, the major changes in response area have involved the I waves, changes in response area of the D waves being of smaller magnitude.

The results of another experiment are presented in graphic form in figure 4, in a manner which allows alterations of response area to be related to the augmented cortical wave.

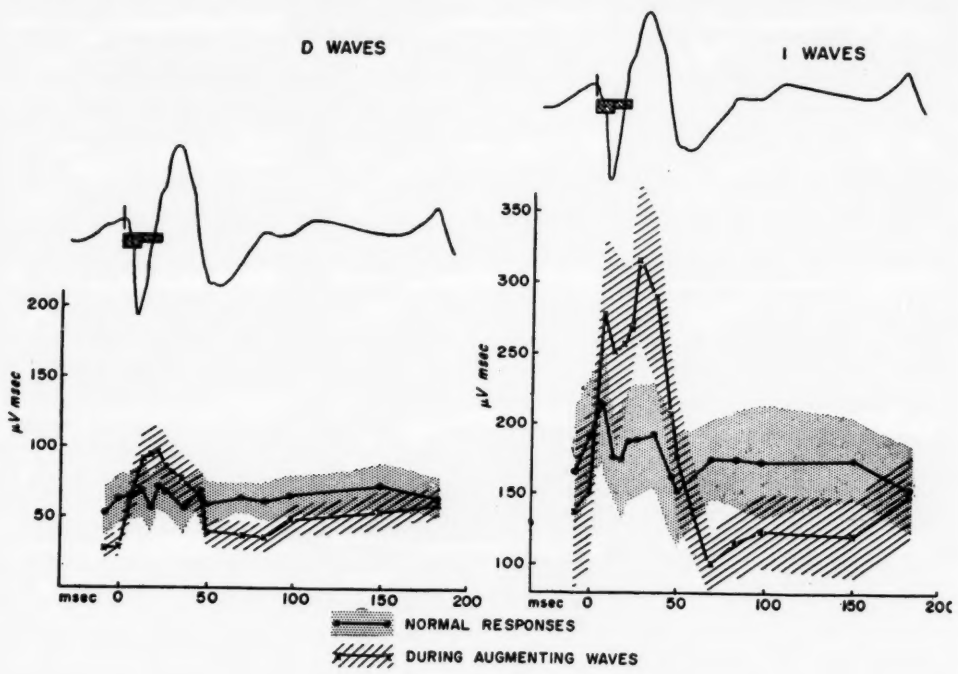


**Fig. 4**

**Unanesthetized cat. Alterations in area of evoked pyramidal D and I waves related to the conditioning augmenting wave. The areas of pyramidal volleys evoked by stimulation of the unconditioned cortex (0.2 msec., 2.0 mA.) are plotted as "normal" responses (•—•). The areas of pyramidal volleys evoked by stimulation of the conditioned cortex are also plotted (x — x). Each plotted point represents the mid-range value of ten superimposed responses. The estimated standard deviation of the individual responses is indicated by the shading and cross-hatching. The augmented cortical response evoked by the last of 5 stimuli to n. ventralis lateralis (0.3 msec., 8/sec.) is drawn to the same time scale at the top of the figure. The small cross-hatched areas on the cortical responses indicate the approximate time of the relayed pyramidal volleys. Note the values of the vertical ordinate (2-4-54).**

Just before the last thalamic stimulus (0 time), the cortical efferent neurones and their related inter-neurones were in a state of reduced responsiveness as indicated by the reduction of D and I response areas below the level of the associated normal unconditioned response. With the appearance of the augmented positivity of the cortical recording, responsiveness increased abruptly to reach a peak during the development of cortical negativity. Increased responsiveness began to

decrease and to pass over into depression coincident with the termination of cortical negativity, depression which persisted for something in excess of 175 msec. following the thalamic stimulus. In all of these experiments, as in those previously described (Zanchetti and Brookhart 1955), the alterations in responsiveness of the elements giving rise to the D wave were much smaller in magnitude than the alterations in responsiveness of the elements giving rise to the I wave. Nevertheless such changes in D wave response area which did occur had the same sign and temporal relations as the alterations in the response area of the I waves.

The changes in responsiveness of the I wave mechanism were manifested primarily through an increase in the duration of the I wave and to a lesser degree through an increase in amplitude. The increase in duration of I activity took the form of the development of a second I wave, with occasional elements of a third showing late in the record. These later I waves always appeared rhythmically, amplitude peaks falling in uniform intervals of 1.5-2.0 msec. The characteristics of these temporal relations gave the impression of reverberating activity in an intracortical circuit or of the addition of one or more synapses in the path between the directly stimulated cells and the cells of origin of the pyramidal fibers.

Diffusely Projecting Nuclei: *Thalamic Mid-Line.* Early in this study it became apparent that in order to study changes in the responsiveness of an efferent system during recruiting responses of the cerebral cortex it would be necessary to take every precaution to avoid the elicitation of mixed recruiting and augmenting responses. Hanbery and Jasper (1953) have pointed out the difficulty of making the distinction between augmenting responses and the short-latency, rapidly-developing responses which may be evoked by stimulation of the more anterior portions of the diffuse projection system such as ventralis anterior and the oral pole of reticularis. Furthermore, the anatomical studies of Nauta and Whitlock (1954) suggest that many fibers from specific thalamic nuclei pass through the lateral and anterior portions of the diffusely projecting nuclei. We considered it highly probable that simultaneous stimulation of these fibers of passage and the cells of the lateral or anterior recruiting nuclei might result in the production of mixed cortical responses of uncertain identity. Nauta and Whitlock (1954) find that the midline nuclei of the diffusely projecting system (reuniens, rhomboidalis, submedius, etc.) send direct cortical projections only to portions of the rhinencephalon and limbic lobe. Any influence which these nuclei have on the sensori-motor cortex must be indirectly relayed (Hanbery and Jasper 1953). We have consequently confined our efforts to elicit recruiting responses to the stimulation of these midline nuclei and have adopted the following as criteria of "pure" recruiting responses: generalized distribution; slow development with little or no response to the first stimulation; latency in excess of 15 msec.; and minimal initial positivity. We regard it as important to bear in mind the restricted sense in which we use the term "recruiting response".

The influence of this type of recruiting activity on the responsiveness of the pyramidal efferent system has been examined in 6 experiments. Recruiting waves, typical of those developing on the sensory motor cortex, are illustrated in figure 2 (middle). The lower tracing in the figure is again a simultaneous recording from the medullary pyramid. In 4 of the animals studied the absence of a relayed pyramidal volley associated with recruiting waves was complete. In 2 preparations, there appeared a questionable relayed volley which barely made itself evident above the noise level. When a pyramidal response was evoked by stimulation of the cortex during the last of the series of 6 to 12 recruiting waves, it was impossible to detect any significant alteration in the evoked response. Recordings from one of these experiments are shown in figure 5. It may be seen that the conditioned responses recorded at various times during the last recruiting wave did not differ in response area from the unconditioned responses shown at the top of the figure. That this lack of alteration in response area was not due to insensitivity on the part of the pyramidal efferent mechanism is proven by the test of cortical sensitivity shown in the lower right and lower left corners of the

figure. The results of the quantitative treatment of the data from another experiment are presented in figure 6. These curves also in-

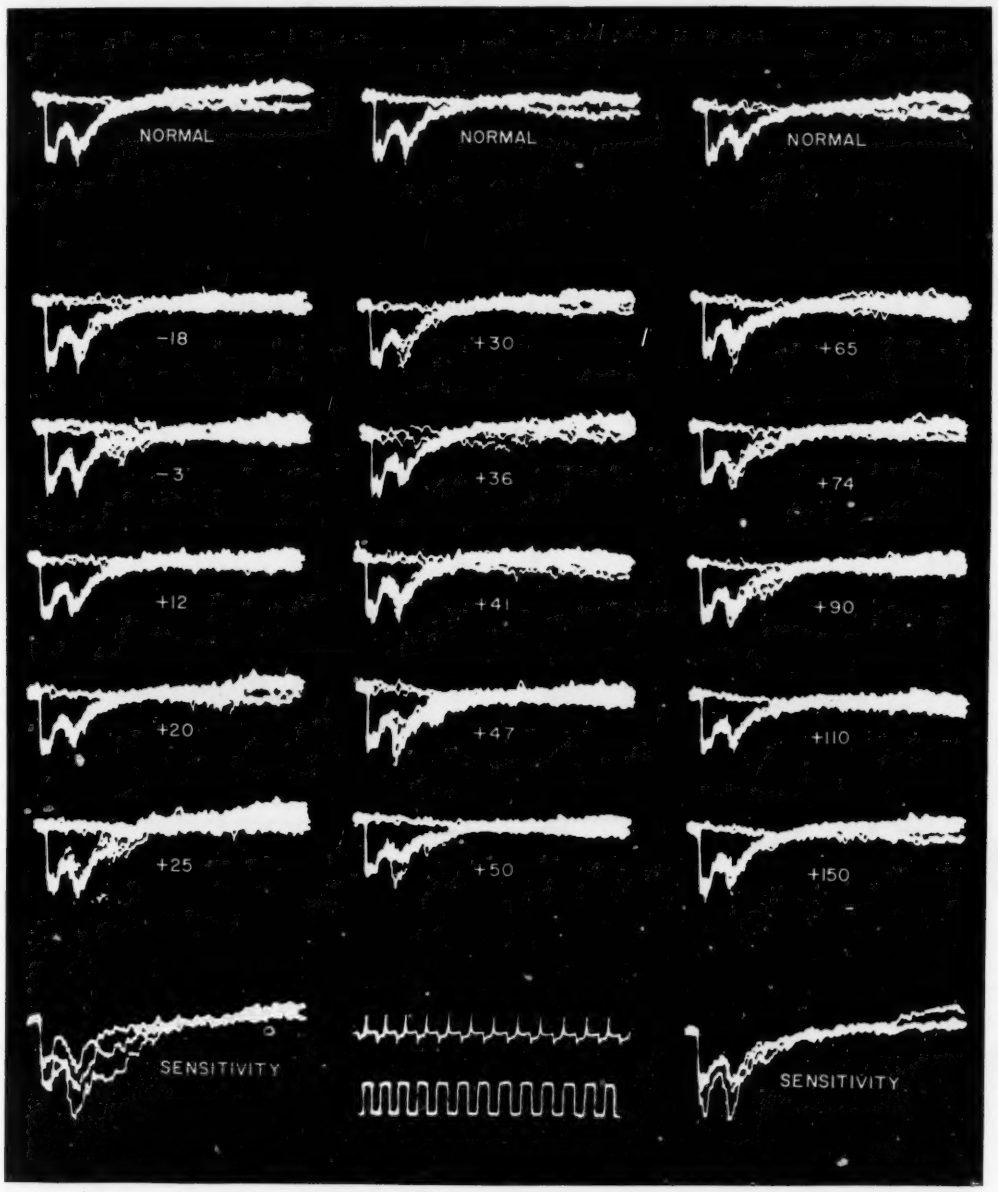


Fig. 5

Unanesthetized cat. Pyramidal volleys evoked by stimulation of the anterior sigmoid gyrus (0.2 msec., 1.75 mA). Normal responses at top of figure. Cortex conditioned by recruiting waves initiated by stimulation of n. centralis, pars medialis (1 msec., 8/sec.). Testing shocks delivered at indicated times before (—) and after (+) the sixth and last thalamic stimulus. Each record consists of 10 superimposed responses. The base lines enclosing response areas were recorded during cortical conditioning but without the elicitation of evoked pyramidal volleys. Lower right: unconditioned responses to pulses of 0.15, 0.2 and 0.25 msec. duration. Lower left: unconditioned responses to pulses of 1.5, 1.75 and 2.0 mA intensity. These sensitivity controls indicate the ability of the system to respond to various parameters of stimulation. Lower center: calibration, 1. msec., 100 $\mu$V. (7-22-54).

dicate that no significant alterations in the responsiveness of the pyramidal efferent system occurred during the course of the recruiting wavé.

Diffusely Projecting Nuclei: *Lateral and Anterior.* Final information regarding the effects of recruitment elicited from nuclei such as centralis lateralis, ventralis anterior, oral pole of reticularis, etc., will have to await further experimentation. It is evident at present that short (8-15 msec.) latency

recruitment waves developing during the stimulation of these structures are sometimes accompanied by relayed pyramidal volleys having a latency comparable to that of the recruitment waves. It also appears that alterations in responsiveness of the pyramidal efferent system comparable to those occurring during augmenting responses may accompany the shorter latency recruiting waves. It has been noted that these recruiting responses are accompanied by a more pronounced initial positivity than are recruiting responses evoked

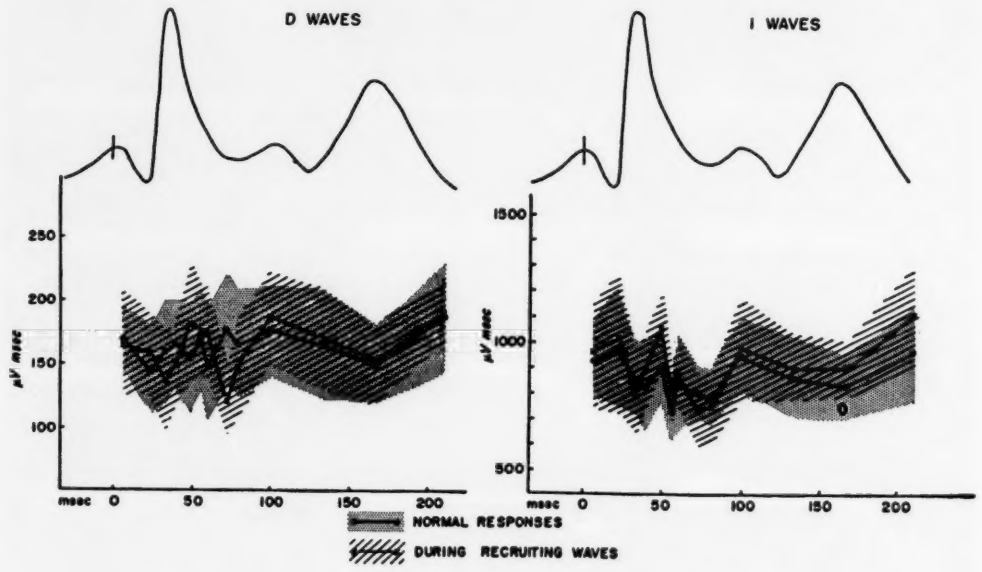


Fig. 6

Unanesthetized cat. Alterations in areas of evoked pyramidal D and I waves related to the conditioning recruiting wave. The areas of pyramidal volleys evoked by stimulation of the unconditioned cortex (0.2 msec., 1.5 mA) are plotted as "normal" responses (●—●). The areas of pyramidal volleys evoked by stimulation of the conditioned cortex are also plotted (x — x). Each plotted point represents the mid-range value of 10 superimposed responses. The estimated standard deviation of the individual responses is indicated by the shading and cross-hatching. The recruiting wave recorded from the anterior sigmoid gyrus as a result of the seventh and final stimulus (1.0 msec., 10/sec.) to the lateral border of centre median is drawn to the same time scale at the top of the figure. Note the values on the vertical ordinates (2-11-54).

of these uncertainties we are uncertain whether ventralis anterior should be regarded as a nucleus of the diffuse thalamocortical system containing fibers of passage from specific nuclei; or as a specific nucleus containing recruiting fibers of passage; or as a source of recruiting responses having different nature and significance from the midline type of recruiting response.

Spontaneous Spindle Bursts. Alterations in the responsiveness of the pyramidal efferent system during spontaneous spindling

from the midline nuclei. Since the nucleus ventralis anterior appears to furnish corticipetal fibers to the sensori-motor cortex (Nauta and Whitlock 1954) of both the "specific" and "unspecific" types (Lorente de Nó 1949), it might be anticipated that the cortical responses would be a mixture of recruitment and augmentation. The situation is rendered more complex by the possibility that fibers of passage from specific thalamic nuclei may course through ventralis anterior and be stimulated along with the cells and fibers taking origin in ventralis anterior. In the face

have also been examined using the recording arrangement described previously. Early in the course of this work, however, it was recognized that wide fluctuations in pyramidal responsiveness characterized these spindling animals. Numerous attempts to relate the alterations in responsiveness to the phase of the cortical spindle wave were totally unsuccessful in that the results indicated a completely random relation between cortical spindle wave and responsiveness. It was eventually recognized that there is a lack of synchrony between spindle waves at individ-

ual points on the cortex, and that many cortical points were not spindling in synchrony with the spindle discharge in the pyramid. The technical modification adopted to overcome this asynchrony consisted of an initial, careful search for that area within the sensorimotor cortex showing the highest degree of correlation between spontaneous cortical spindle and relayed pyramidal spindle. This cortical focus was then used for the application of test stimuli at different phases of the relayed pyramidal spindle. With the adoption of the relayed pyramidal discharge as the basis for the timing of the testing shock to the cortex, a relationship between pyramidal relayed volley and responsiveness emerged.

Careful study of EEG and oscillographic records made it possible in 9 animals to find a focus for the monopolar recording electrode which revealed a fixed relationship between the cortical spindle wave and the relayed pyramidal volley. Furthermore, even though the relayed pyramidal volley sometimes appeared on an unstable baseline, the initiation of the relayed volley could reliably be taken as an inflection or shoulder where the rate of change of voltage suddenly increased toward positivity. Correlations of this kind indicated that the spindle wave began with an initial positive swing. Some milliseconds after the beginning of cortical positivity, the relayed pyramidal volley appeared at the medullary level. It was the uniformity of this relationship which permitted the correlation between responsiveness of the pyramidal efferent system and cortical spindle wave, even though the relayed pyramidal spindle was used to time the testing shock to the cortex.

It deserves to be pointed out that a number of our preparations had to be discarded because of a dissociation between surface electrical activity and relayed pyramidal discharge. The persistence of surface electrical activity during the absence of relayed efferent volleys has been noted previously (Adrian and Moruzzi 1939). It was our impression that the cessation of relayed pyramidal activity occurred very early in the course of deterioration of the preparations. A similar dissociation could be produced at will through the administration of anesthetic agents. In such preparations parallel evidence of cortical deterioration was seen in the form of an increase in threshold, diminution of sensitivity, and increase in stability of electrically evoked pyramidal responses. The results to be described here were all obtained from pre-

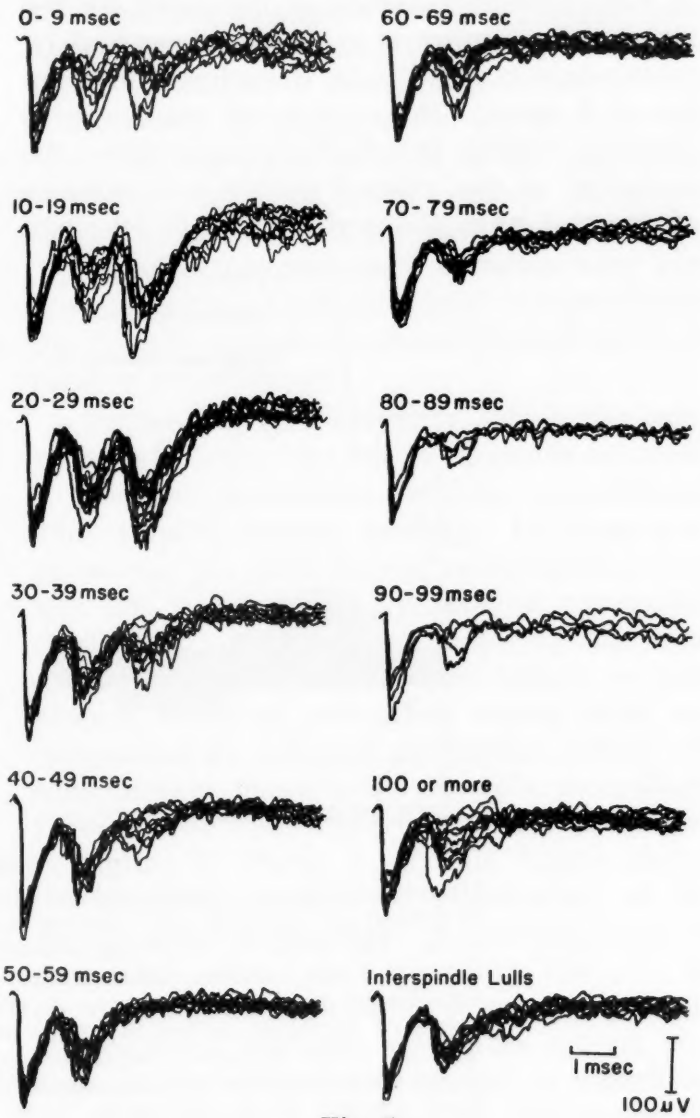


Fig. 7

Unanesthetized cat. Mesencephalic thermocoagulation. Pyramidal volleys evoked by stimulation of anterior sigmoid gyrus (0.2 msec. 1.5 mA). A large number of records were taken at various times after the initiation of relayed pyramidal spindles. The individual responses were classified as to time of occurrence after the initiation of the associated cortical spindle wave and traced in superimposed fashion. Responses evoked during spindle waves are to be compared with responses evoked during interspindle lulls (6-28-54).

parations in which these evidences of cortical deterioration did not occur.

The changes in the size of evoked pyramidal volley which occur during different phases of a single cortical spindle wave are illustrated in figure 7. Superimposed traces from volleys evoked during interspindle lulls

are shown in the lower right and reveal insignificant changes in cortical responsiveness during such periods. In the time interval from 0 to 9 msec. after the beginning of the relayed pyramidal volley an abrupt increase in responsiveness occurs as indicated by the increase in amplitude of the D waves and by an increase in amplitude, duration, and number of I waves. Responsiveness continues to augment during the first 30 msec. after the initiation of the relayed volley and remains augmented until the period from 50-59 msec. addition to those activated by the spindle mechanism. The spontaneous nature of the spindle burst made it impossible to stop the spindle waves abruptly, thus making it impossible to follow to completion the uncomplicated recovery of responsiveness from the depression which occurred between spindle waves.

Data from a similar experiment are presented in graphic form in figure 8. As was the case in earlier figures, the changes in response area are plotted on a time base which

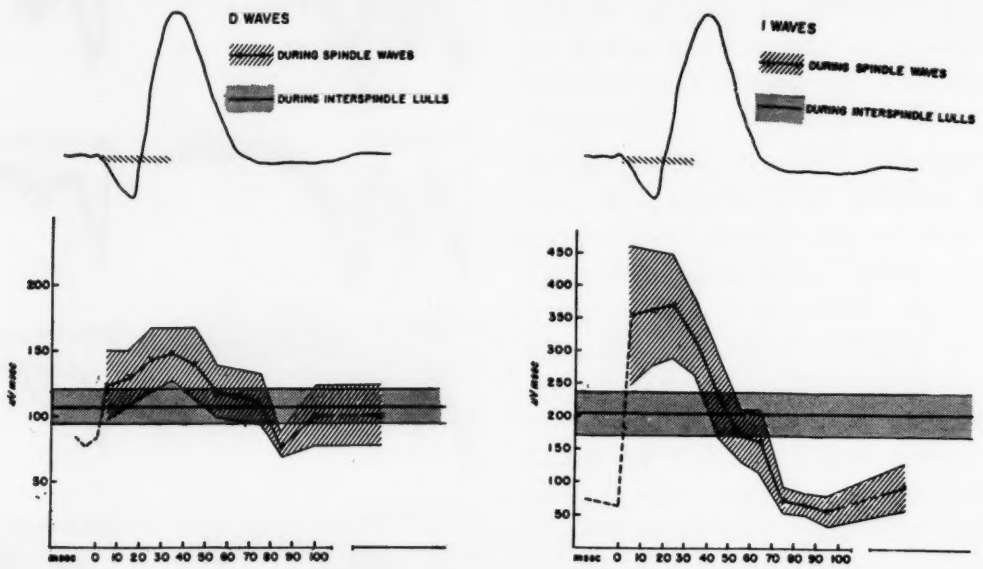
D WAVES
DURING SPINDLE WAVES
DURING INTERSPINDLE LULLS
I WAVES
DURING SPINDLE WAVES
DURING INTERSPINDLE LULLS
msec 0 10 20 30 40 50 60 70 80 90 100

Fig. 8

Unanesthetized cat. Mesencephalic thermocoagulation. Alterations in areas of evoked pyramidal D and I waves related to the associated cortical spindle wave. The areas in responses evoked by stimulation of the cortex (0.15 msec., 1.5 ma.) during interspindle lulls during various portions of the experiment were considered as a single group, and the mid-range and standard deviation indicated as the solid horizontal line and shaded area. The mid-range values of responses evoked during various phases of spindle waves are also plotted and the standard deviation indicated by cross-hatching. Each plotted point represents 10-20 responses. A typical spindle wave from the anterior sigmoid gyrus is drawn to the same time scale at the top of the figure. The timing of the spontaneous volley relayed to the pyramid is indicated by the small cross-hatched area on the spindle wave (7-8-54).

Thereafter, a period of reduced responsiveness ensues which endures until the onset of the subsequent spindle wave at approximately 80-100 msec. It is to be noted that at the sweep speeds used for these recordings, the time course of the relayed pyramidal volley was such that, recorded with a decreased time-constant, it was revealed only as a slight shift of the baseline upon which the evoked response is recorded. Therefore, as was the case with augmenting waves, the evoked volley represents discharge from a population of neurones which are activated by the shock in permits correlation with the changes in cortical potentials during a spindle wave. Here, the baseline with which the areas of conditioned response are to be compared consists of the areas of responses evoked during interspindle lulls at various times during the course of the experiment. It is evident from these curves that the facilitation of cortical responsiveness begins during the initial positivity of the spindle wave and continues somewhat past the peak of the subsequent cortical negativity. The later phases of cortical negativity and the period between two adjacent

spindle waves is characterized by a period of depressed responsiveness which is abruptly terminated with the onset of the subsequent spindle wave. It is perhaps significant that the period of the relayed pyramidal volley as denoted by the cross-hatched area on the cortical electrogram does not coincide precisely with the period of facilitation of the pyramidal efferent system.

Recruitment and Spindle Interaction. It will be recalled that these studies of the effects of recruiting activity on the responsiveness of the pyramidal efferent system were carried out on unanesthetized animals in a state of electrocortical arousal. Jasper (1954) has suggested that it is inadvisable to contrast changes in cortical responsiveness in an aroused animal with alterations of responsiveness in a spindling animal since the basic state of the cortex may be entirely different in the two conditions. In support of this suggestion it will be recalled that Moruzzi and Magoun (1949) revealed the ability of activity induced in the brain stem arousal system to prevent the development and block the appearance of recruiting waves. It must be admitted that even though the intensity of arousal influences in our unanesthetized animals may have been insufficient to block completely the development of recruiting waves, it could have blocked their effect upon other intracortical systems. It may be that if influences from the arousal system had been eliminated by mesencephalic coagulation, thus producing a spindling cortex, the recruiting mechanism would have been able to influence other intracortical systems.

In order to test this possibility, several experiments were performed in the following fashion. Recruiting responses were elicited in the usual fashion by stimulation of the midline nuclei in unanesthetized animals. As in earlier experiments these were unaccompanied by relayed pyramidal discharge. Following this, without moving the thalamic stimulating electrode, the animals were subjected to mesencephalic thermocoagulation in order to convert them to the spindling state. Using the same focus for stimulation and the same stimulus parameters, recruiting responses were again elicited while recording from the pyramid.

Two sorts of difficulties were encountered which prevented the results of many of these experiments from being informative. One of these difficulties hinged upon the well-known "spindle-tripping" propensity of stimuli to the midline thalamic nuclei (Jasper and Droogleever-Fortuyn 1947). Thus, it was difficult to initiate a train of thalamic stimuli which would be adequate for the development of recruiting waves without at the same time tripping a burst of spindle waves. A second difficulty arose from the fact that often the "pyramidal preparation" spindles very vigorously, with interspindle lulls of insufficient duration to permit the uncomplicated development of recruitment.

In three preparations, in which the mesencephalic lesion was not as extensive as usual, a clear-cut separation between recruitment and spindles became evident. In these preparations, the elicitation of recruitment waves was not accompanied by relayed pyramidal discharges. On the other hand, spontaneous spindle bursts, occurring just before or just after a series of recruiting waves, were accompanied by relayed pyramidal volleys of considerable magnitude. Sample recordings from one of these experiments are presented in figure 9. Strip A of this figure shows the predicted results of stimulation of N. reuniens and submedius; the development of recruiting waves approximating 750 $\mu$V. in amplitude; and the absence of relayed pyramidal activity. Shortly after this record, the animal was left for some period in a darkened, quiet room. At the end of this period of inactivity, spontaneous spindle bursts were appearing at infrequent intervals. Strip B shows one of these spontaneous bursts, accompanied by relayed pyramidal activity, followed by a group of evoked recruiting waves. Shortly after this recording the animal was converted to a pyramidal preparation by mesencephalic thermocoagulation. Strip C was recorded after this procedure and shows a group of recruiting waves initiated by thalamic stimulation, followed almost immediately by a "tripped" spindle burst. Strip D shows the reverse sequence, — a spontaneous spindle burst during the course of which a train of thalamic stimuli was initiated. As judged by the relayed pyramidal volleys, the

recruiting waves outlasted the spindle burst. The association of spindle waves with relayed volleys and recruiting waves with pyramidal inactivity is clearly demonstrated in these records. Furthermore, the initial state of the preparation apparently does not alter these relationships.

It will be noted that in these recordings, the recruitment waves are often accompanied by minor disturbances of the pyramidal recording. In view of the fact that tip separation of the recording electrodes was adequate to raise the shell of the electrode into the reticular formation when the tip of the core was in the pyramid, it was considered possible that these minor, prolonged potential fluctuations resulted from activity in the reticular formation overlying the medullary pyramid. Such reticular activation could be the result of impulses descending from the diencephalon over extrapyramidal pathways which were spared by the mesencephalic thermocoagulation. Evidence in favor of this interpretation was obtained from the same preparations by elevating the pyramidal electrode 2.0 mm. In this position, relayed pyramidal volleys were not recorded during spindling, but the small potential fluctuations continued to develop during recruitment.

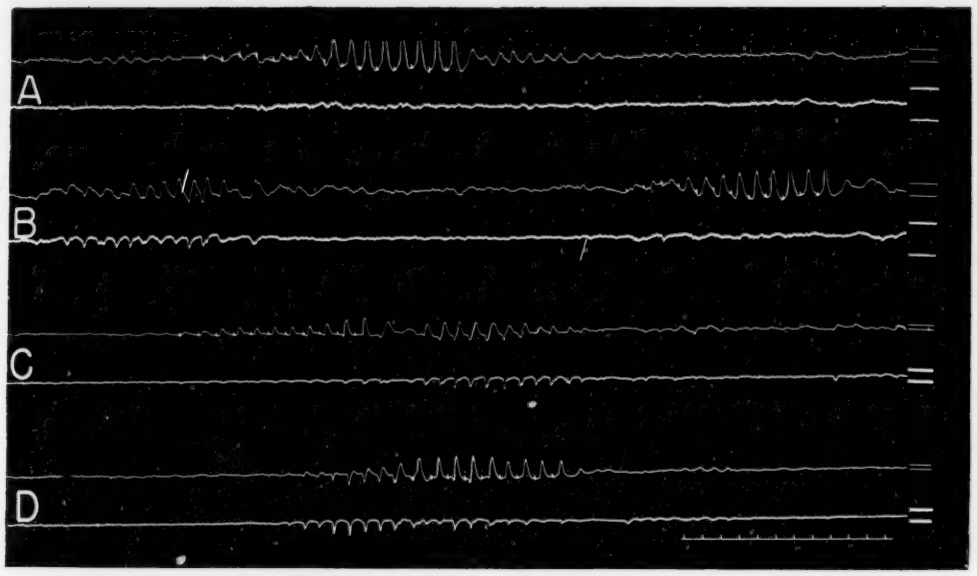


Fig. 9

Unanesthetized cat. Comparison of pyramidal activity during spindling and recruitment. Upper line: Anterior sigmoid gyrus. Lower line: Medullary pyramid. A. Recruting responses evoked by stimulation of N. reuniens and submedius. Note absence of relayed pyramidal activity. B. Several minutes later, the preparation began spindling during a period of quiet in the laboratory. A spontaneous spindle burst is shown, followed by a series of evoked recruiting waves. C. Same animal after mesencephalic thermocoagulation. The thalamic stimulating electrode has not been moved. A series of recruiting waves is followed by a tripped spindle burst. D. A series of recruiting waves is initiated during a spontaneous spindle burst and prolonged beyond the end of the burst. The small fluctuations in the pyramidal recording during recruitment were due to activity in more dorsal portions of the medulla, for they persisted when the electrode was raised until its tip lay at the dorsal border of the olivè. In this position relayed pyramidal volleys could not be recorded during spindling. Sensitivity calibrations at right end of each strip — 250 $\mu$V. Time at lower right — 100 msec. (12-30-54).

## DISCUSSION

The results of these experiments may be summarized in a few simple statements. In unanesthetized animals, a single thalamocortical volley originating in ventralis lateralis, ventralis postero-lateralis or ventralis postero-medialis has little, if any, effect upon the responsiveness of the cells of origin of the cortico-spinal fibers or upon their related cortical interneurones. If, by low-frequency repetitive stimulation of the same thalamic focus, the additional thalamic or cortical activities which give rise to the augmenting re-

sponse are called into play, the responsiveness of the same group of cortical neurones undergoes periods of augmentation and depression which are temporally related to the cyclic changes of surface potential. Fluctuations in responsiveness that are, in all observed respects, comparable to those occurring during augmenting responses also occur during spontaneous spindle waves. Those forms of cortical response which are accompanied by fluctuations of responsiveness are also accompanied by relayed pyramidal discharges. On the other hand, recruiting responses initiated by stimulation of the midline thalamic components of the diffuse thalamic projection system produce no effect on responsiveness in the neurones of this cortical efferent system, nor are they accompanied by relayed pyramidal volleys. Thus, despite the similarities which are noted among these three types of electrocortical activity, the uniqueness of the mechanism producing the recruiting responses is unquestionable. It is unfortunate that the short-latency, fast-developing recruiting responses elicited by stimulation of the more cephalic portions of the diffuse thalamic projection system cannot, in the lack of adequate anatomical information, be defined either as pure recruiting responses or as mixed recruiting and augmenting responses.

It would appear that three items of additional information are still required which are essential to a complete understanding of the reasons for the results reported here. First, it is essential to know the nature and the terminal distribution of the cortical afferents which are involved in the production of these various forms of electrocortical activity. It is commonly accepted (Perl and Whitlock 1955; Bishop and Clare 1953; Chang 1952) that the "specific thalamic afferents" described by Lorente de Nó (1949), terminating in bushy endings in the third cortical lamination, underly the initiation of the response of the sensori-motor cortex to single thalamic or sensory volleys. Whether these are also the afferents which are responsible for the added elements of the augmenting response and for the spindle waves is unknown. It has been suggested by Morison and Dempsey (1942b) that recruiting responses might be initiated in the cortex by activity conveyed over the "unspecific thalamic afferents" described by Lorente de Nó (1949). The anatomical studies of Nauta and Whitlock (1954) neither support nor refute this suggestion. Secondly, it is essential to acquire a better understanding of the significance, in terms of intracortical events, of the various phases of surface potential change. The studies of Bishop and his collaborators (1953) have contributed significantly to our understanding of the surface potential change occurring at the visual cortex as a result of volleys in the visual afferents. It is not known that the same interpretations can be transferred *in toto* to the varieties of potential change under consideration in this study. And, thirdly, it is essential to understand the identity of the cortical neurones involved in these responses and the manner in which activity in various afferents may be transferred to these neurones. Without these essential items of information any attempt to explain these results must be purely speculative in nature. Nevertheless, some speculation at this point seems worthwhile in order to guide future experimentation.

Some attention should be paid to the possibility that the changes in responsiveness noted during these studies may have resulted, not from the direct actions of nerve impulses impinging upon synaptic junctions, but from the establishment of potential fields and flow of current which influence responsiveness by polarization or "ephaptic" effects. This sort of possibility has been given serious consideration in another connection by Adrian (1949). It receives further emphasis as a result of several recent studies of the effects of polarization upon neuronal behavior (Burns 1953; Brookhart and Blachly 1952; Goldring and O'Leary 1951). If an attempt to explain altered responsiveness on the basis of polarization effects is based on the somewhat naive assumption that all similar patterns of surface potential change are representative of similar patterns of intracortical current distribution, such an attempt fails at the outset. Some recruiting waves are indistinguishable in form from spindle waves. One is accompanied by relayed pyramidal volleys and altered responsiveness, while the

other is not. If the intracortical current distribution is the same in both cases, then polarization cannot explain both situations. On the other hand, it is not inconceivable that different patterns of current distribution within the cortex may be accompanied by similar surface potential changes. Indeed, the different patterns of potential distribution in the depths of the cortex accompanying specific and recruiting responses (Jasper 1954) can only mean that patterns of current flow differ in the two situations.

Taking the other point of view, — that these alterations in responsiveness are due to transynaptic activation of cortical neurones, — two different hypothetical explanations of these observations may be attempted. It is possible that the different effects of augmenting and spindling waves as contrasted to recruiting waves are due to the involvement of two functionally and anatomically distinct groups of neurones. It is alternatively possible that the various effects are due to the arrival of corticipetal impulses at different portions of the same group of cortical neurones. As the basis for a working hypothesis to be tested in future experiments we are currently assuming that, (1) corticipetal fibers initiating recruitment differ in their termination from those producing spindling and augmenting waves; (2) the recruiting fibers influence the apical dendrites of pyramidal cells whereas the spindling and augmenting fibers influence the basilar dendrites and somata of these same cells directly and through the agency of the Golgi type II cells of the third and fourth layers of the cortex.

The characteristics of the evoked pyramidal response support the notion that deep cortical interneurones (Burns and Grafstein 1952) are included in the response to stimulation of specifically projecting thalamic nuclei. It is obvious from an examination of these records (fig. 3,4,7 and 8) that the I waves are significantly more labile than the D waves. It follows that the influences which augment responsiveness operate more forcibly on cortical interneurones than on the pyramidal cells of the fifth layer or their dendritic extensions. These interneurones command a larger population of fifth-layer cells than does the electrical stimulus. This is concluded from the fact that the I wave response area is so often larger than the D wave response area, and suggests the operation of a mechanism leading to intracortical spread of response. Furthermore, this facilitatory influence is noteworthy for the manner in which it can produce repetitious formation of the I wave pattern. It is impossible to say at present to what extent these repetitious volleys originate from a common population of efferent neurones. Patton and Amassian (1954) have observed situations in which a given pyramidal axon was identified solely with the D wave, another solely with the I wave, and others identified with both elements of the complex. It is considered highly improbable that repetitive I waves are due to activity in a thalamo-cortico-thalamic reverberating circuit. The peak-to-peak interval of 1.5 to 2.0 msec. would appear to be too brief to allow for two directions of conduction and two nuclear delays. Indeed, in all instances where such reverberating circuits have been used to explain observed phenomena (Forbes, Battista, Chatfield and Garcia 1949; Chang 1950; Dempsey and Morison 1942a) the repetition interval under consideration has been of the order of 100 msec.

The depressed responsiveness of neurons of the pyramidal efferent system occurring between spindle waves and after the last of a series of augmenting waves is not seen in relation to recruiting waves. Three different mechanisms must be considered as possible causes of this depressed responsiveness, namely, (*a*) refractoriness, (*b*) inhibition, or (*c*) subnormal excitability. We are inclined to dismiss the idea of depressed responsiveness resulting from refractoriness of the elements involved. If the depressed phase were the result of refractoriness on the part of the cells of this system, it would seem that it should develop more abruptly, disappear more suddenly, and show a closer temporal relationship to the relayed discharge. Rather, it develops gradually, long after the relayed discharge is completed, and persists for as long as 200 msec. after a terminal thalamic stimulus. It is conceivable that the depression may be the result of an inhibitory influence which is weaker and more prolonged than the antecedent facilitatory activity. If it can be

considered that cerebral neurones have behavior characteristics like those of spinal cord motor neurones (Brooks *et al.* 1950; Brock *et al.* 1952) it is then necessary to admit the possibility that this depression is coincident with the subnormal phase of the recovery cycle of the neurones involved. It would be predicted that such subnormality would augment upon repetitive excitation and that the diminution in excitability would be prolonged, in part by the augmentation and in part by the increasing degree of asynchrony in the population of cortical neurones involved. Necessary information which would permit a selection between these two possibilities is not available at present.

These results appear to have made more apparent certain points which have been previously disregarded or poorly understood. The difference between the single evoked response and the augmenting response of specific projection areas, and between the augmenting and recruiting response, has been re-emphasized after having been too often neglected. It is highly possible that the difference between the results reported here and the results reported by Arduini and Whitlock (1953) is dependent upon their utilization of a response which was a mixture of augmentation and recruitment. The necessity for using extreme care in making this differentiation when studying the diffuse thalamic projection system cannot be overemphasized. It has previously been suggested that recruiting waves and spontaneous spindle waves are identical phenomena employing a common set of cortical afferents (Arduini and Whitlock 1953; Dempsey and Morison 1942b). In view of the distinct differences between the effects of these two types of cortical activity on the pyramidal efferent system of neurones, it would appear that this conclusion should be examined more closely. Since so little is known about the mechanisms underlying the origin of spindle waves and conditioning their sporadic appearance a further analysis of the differences seems unwarranted at this item. The possibility must not be overlooked that spindle waves may be related to the more anterior and lateral portions of the diffuse thalamic projection system.

SUMMARY

1. Studies of the responsiveness to electrical stimulation of the system of cortical neurones giving rise to evoked volleys in the medullary pyramid have been carried out in cats.

2. Phasic variations in responsiveness and relayed activity have been correlated with phasic changes of cortical surface potential during the elicitation of augmenting waves and during spontaneous spindle waves. Relayed pyramidal volleys appear during the initial surface positivity of each of these cortical wave forms. During the positive and early negative phases of the surface potential waves, the responsiveness of the efferent neurone system is augmented. During the late phase of cortical negativity, and for 50-150 msec. thereafter, responsiveness of the efferent neurone system is depressed. These changes affect the indirect portion of the evoked pyramidal volley to a significantly greater extent than the direct portion of the volley.

3. Responsiveness of this corticifugal neurone system has also been tested during the elicitation of that particular form of recruitment wave which develops upon stimulation of the midline nuclei of the diffuse thalamic projection system. During this type of recruitment response there is no relayed pyramidal volley. Neither is there any detectable alteration in responsiveness of the efferent neurone system.

4. The marked differences in the effects associated with these electrically similar potential changes indicate the existence of at least two fundamentally different mechanisms subserving thalamo-cortical relationships.

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# AN ANALYSIS OF THE CORTICAL RESPONSE TO ANTIDROMIC PYRAMIDAL TRACT STIMULATION IN THE CAT[1]

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The earliest study of the cortical potentials resulting from antidromic stimulation of the pyramidal tract in the medulla is that of Woolsey and Chang (1948). They were particularly interested in the surface distribution of potentials as a method for defining the origin of the pyramidal tract; the monkey, dog, and rabbit were studied in addition to the cat. In the last they report a rather variable pattern of response. They note that it was possible to get sufficient current spread through the pyramid to activate the underlying medial lemniscus and a consequent dromic cortical response. Such complication was avoided by stimulus strength adjustment and "by taking advantage of the fact that evoked afferent responses of the cortex are unable to follow rapid rates of stimulation because of increased refractoriness in the thalamus". They note the shorter latency of true antidromic responses and state that they used the controls of sectioning the pyramid above the stimulus and of sectioning the midbrain except for the peduncle. They report widespread antidromic responses covering in the cat the entire sigmoid gyrus and a portion of suprasylvian and ectosylvian gyri. It is not clear how the controls mentioned above affected the surface distribution of antidromic potentials or the calculated distribution of fiber sizes in the pyramid derived from the deflections of cortical potential.

Lance and Manning (1954) repeated this study and generally confirmed it. They recorded intracortically with fine electrodes and mapped the spike distribution "rather than the slow potential changes recorded superficial and deep to cell layers which are caused by widespread electrical fields and can so easily be confused by the activity of medial lemniscus". They thus infer that spikes, regardless of latency, are, in the absence or relative absence of slower oscillations, a sign of true antidromic activity. They point out, as is apparent from their records, that it is not possible entirely to exclude the dromic response even by tetanic stimulation. Recently Porter (1955) has also confirmed the work of Woolsey and Chang with surface leads. He states that dromic activity due to current spread can be identified by tetanic stimulation at 10-30 per sec. or by use of anoxia.

Still more recently Chang (1955a and b) has given further attention to the antidromic response in the rabbit. He does not mention the problem of lemniscus stimulation and infers that his records show synaptic activation of cortex by the recurrent collateral fibers of pyramidal neurons.

The present study was initiated by the chance observation that the response in posterior sigmoid gyrus to presumed pyramidal tract stimulation is identical in form to response in visual cortex following optic nerve stimulation. It was also considered likely that the antidromic activation of cortical neurons might furnish a useful tool for study of cortical dendrites.

## METHOD

The results here reported comprise experiments on 47 adult cats under light Surital (thiamylal sodium) anesthesia. The sigmoid and perisigmoid cortex was usually exposed bilaterally. The ventral medullary surface was exposed for superficial pyramidal tract stimulation; a dorsal exposure of the posterior fossa was used in other experiments where electrodes were inserted through the medulla.

[1] This work was supported in part by United States Public Health Service grant B-882.

When the lemniscus was to be severed the midbrain was first exposed by removal of one occipital pole and hippocampus.

Square pulses of 0.2 msec. duration passed through an isolation transformer were used routinely for stimulation. The transformer output was directed into a Wagner tripolar electrode arrangement, one electrode connected to the center tap of a 1 meg. potentiometer. In addition, to control shock artifact it was useful to connect a variable resistance-capacity to ground from one or the other stimulating lead. For superficial cortical or medullary stimulation the electrode consisted of silver wires 1.0 mm. apart. Monopolar stimulation in the medulla was performed with a 75 mu steel wire; similar anode and variable leads could be placed at random. In practice it proved convenient for artifact control to attach these to the same chassis as the cathode so that they moved with it. They were thus situated usually in and ventral to the lateral portion of the medulla. Controls indicated that response patterns were similar when these leads were in the cervical soft tissue.

All cortical recording was bipolar in a plane normal to the cortical surface. Routinely the leads were a pair of 75 mu steel wires 2.0 mm. apart, one on the surface and one in the subcortical white matter. For special analysis as many as 6 were mounted together, the tips separated by 0.5 or 1.0 mm. A double beam oscilloscope with resistance-capacity coupling was used routinely; DC recording was used in some experiments.

When the medullary electrode was inserted from the dorsal surface, the corticospinal tract was identified by the response to anterior sigmoid stimulation. The locus was always checked subsequently by Marshall's technique (1940) and was correct without exception. Similar histological control was used for the cortical electrode placements.

The pyramidal tract was sectioned with a fine hand ground razor blade; it was never possible to sever it without some degree of injury to the adjacent lemniscus; the experiment in figure 4 B, C is the best of many attempts. The lemniscus was severed in the midbrain with a spatula while monitoring the responses in both sigmoid gyri. The extent of midbrain and medullary lesions was checked by dissection and hand section on the fixed brains.

Drugs used for topical application were veratrine hydrochloride 0.1 per cent in Tyrodes and strychnine sulfate 0.5 per cent in Tyrodes.

## RESULTS

Figure 1 A shows the typical response of the lateral portion of anterior sigmoid gyrus to medullary pyramidal tract stimulation. The latency of the initial spike is 0.75 msec. This is usually the same or up to 0.1 msec. more than the latency of the dromic response to cortical stimulation recorded monopolarly in the medulla. Following this monophasic 1.3-1.4 msec. spike, which certainly is thus assignable to antidromic conduction in the fastest pyramidal fibers, there is a 4-6 msec. positive wave and a subsequent 12-20 msec. negative wave. Minor irregularities may occur on the positive wave which is somewhat less constant than the preceding spike. The excitability cycle series shows that the positive spike is recovered in 2 msec. and that the inflection of the positive wave from the second shock is also present (fig. 1 A, 2). The response to the second shock is practically completely recovered by 6 msec. Note the potentiation of the negative wave when the stimuli are close together. The fact that the positive wave does not occlude the spike from the second shock indicates that wave and spike are due to discharge in different neurons, or at least different parts of the same neurons. It is likely that the positive spike and wave represent the major fiber groups of the pyramid (Brookhart 1950; Bishop, Jeremy and Lance 1953; Lance 1954; Lance and Manning 1954).

Figure 1 B is a typical response from the posterior sigmoid gyrus. The latency is 1.4 msec., consistently longer than that in the anterior sigmoid. The response consists of three major positive spikes with a fourth often evident as a deflection on the descent to the subsequent negative wave. A minor small spike is sometimes apparent between the first and second major spikes. The entire re-

sponse is indistinguishable from the response of visual projection cortex to synchronous activation of the optic pathway (Bishop and O'Leary 1938; Marshall, Talbot and Ades 1943). The first spike may thus be assigned to the thalamic radiation fibers entering the cortex; the subsequent components are presumably due to serial and perhaps repetitive activation of intracortical neurons (Bishop and Clare 1951, 1952, 1953a and b; Landau and Clare 1956). The prolonged recovery cycle evident in the two shock series supports the view that this pattern is projected synaptically via the thalamus (Marshall 1941, 1949). The simplest explanation of this finding is that stimulating current has spread to the medial lemniscus beneath the corticospinal tract.[1]

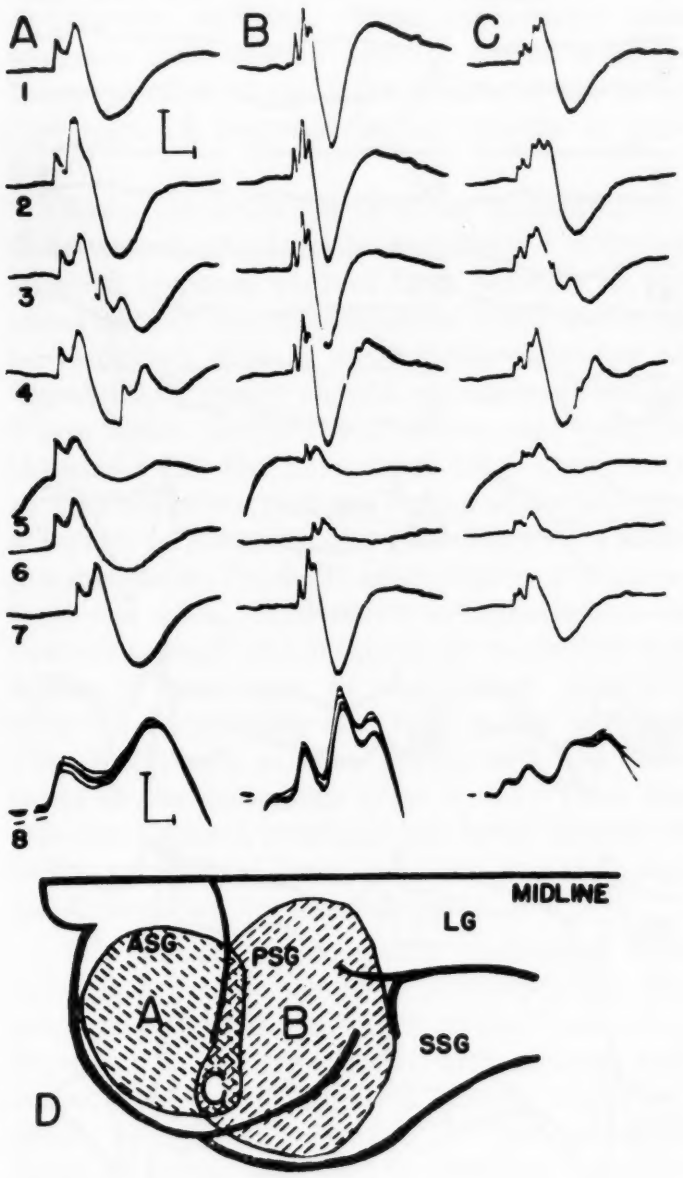


Fig. 1

A. Response in anterior sigmoid gyrus to surface stimulation of medullary pyramid. Single shock in (1). Subsequent traces show response to second shock at progressive intervals, 1.2 sec. cycles (2). 2 msec. (3). 6 msec. (4). 10 msec. (5). 15 msec. (6). 100 msec. (7). 200 msec. (8). Superimposed traces at 2 sec. intervals with faster time base. B. Response from posterior sigmoid gyrus as in A. Note delayed recovery compared with A. C. Response from area lateral to cruciate sulcus, mixture of A and B. D. Diagram of general areas from which responses are obtained, approximate maxima at letters A, B, C. ASG — anterior sigmoid gyrus. LG — lateral gyrus. SSG — suprasylvian gyrus. Surface electrode positive is up in all figures. Calibrations 200 $\mu$V. and 5 msec. in 1-7; 100 $\mu$V. and 1 msec. in 8.

In the cortical area between those giving these two patterns, the response (fig. 1, C) appears to be a mixture of the two. The radiation spike and subsequent dromic response have a delayed recovery and thus expose the rapidly recovered antidromic response which apparently includes all three components seen in figure 1, A.[2]

Figure 1, D indicates the general areas in which responses were found. Detailed mapping was not the object of this study and the outer border areas were checked in only a few animals. The distribution of the antidromic spike posterior to the cruciate sulcus was examined closely, not only in the intact animals but also after transection of the lemniscus. The posterior sigmoid antidromic response near the sulcus ranged from nothing to as much as a third of the maximal response in locus A. There was some indication that this individual variation related to the depth of the sulcus. There was no significant antidromic response in posterior and posterolateral posterior sigmoid or in the adjacent suprasylvian gyrus. On a few occasions here

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[1] Although Brodal and Kaada (1953) have claimed that there are ascending afferent potentials in the pyramidal tract, it has been shown that they were dealing with spread of action currents from the subjacent lemniscus (Landau 1956).

[2] It is always difficult to measure accurately the spike heights of the second response on the polyphasic baseline of the first, hence there is often some degree of uncertainty about the early phase of recovery where spikes overlap. This feature is particularly prominent for the antidromic (first) spike in figure 1, C 2, 3, and suggests that there may be some true occlusion between the spikes of the first shock dromic response and the second shock antidromic spike. As will become evident, detailed study of this phenomenon would require transection of the lemniscus and separate stimulation of pyramid and thalamic projection.

after presumably complete section of the lemniscus there persisted a small late slow positive-negative potential that might be assigned to slow pyramidal fibers. This was seen too seldom for detailed study.

Repetitive stimuli at various frequencies (fig. 2 A-C) confirmed the findings of the double shock series; the anterior sigmoid response follows without significant decrement

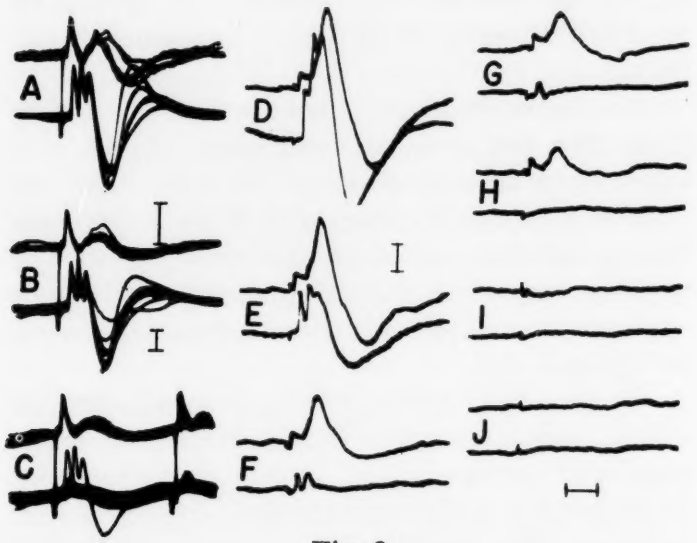


Fig. 2

A. Superimposed responses to pyramidal tract stimulation in anterior sigmoid (upper trace) and posterior sigmoid (lower trace) at ½ sec. B. Same at 5/sec. C. Same at 50/sec. Anterior sigmoid response follows well at higher frequency. D-J another preparation. Control in D after which trachea was occluded. Late positive wave in upper trace unusually large. Subsequent traces at: E. 1 min. Depression of posterior sigmoid and late anterior sigmoid response. F. 2 min. Progression; 2 spikes in posterior sigmoid. G. 2½ min. "Radiation spike" in posterior sigmoid. H. 3½ min. Posterior sigmoid response out. I. 4½ min., trace of spike in anterior sigmoid. J. 7½ min. No response. Calibrations 200 $\mu$V. and 5 msec.

at 50 per sec. when the posterior sigmoid response is grossly depressed. It is noteworthy however that the latter is still present up to 200 per sec.

Anoxia is a tool of some value since Noell and Chinn (1950) have shown that it depresses the cortical stage of the visual system first, followed by the serial depression of the more distal structures. Pathways without synapses are generally believed to withstand anoxia longer than relay systems. Figure 2 D-J shows that anoxia first depresses the posterior sigmoid response and the anterior sigmoid positive and negative waves. This

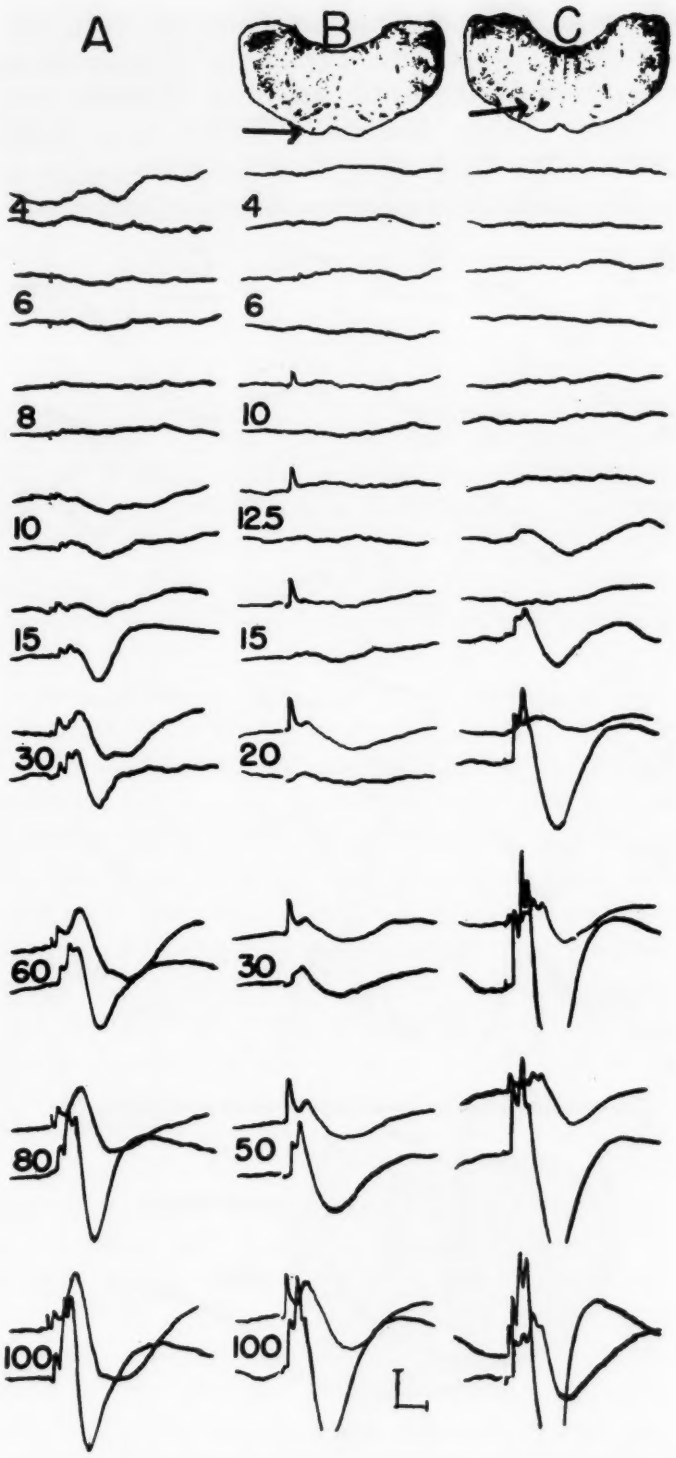


Fig. 3

A. Surface stimulus on medullary pyramid. Upper trace is anterior sigmoid and lower, posterior sigmoid response to increasing voltage. Arbitrary voltage scale values are indicated. Note that responses have no detectable difference in threshold. B. Another preparation. Response to increasing shocks applied to marked locus in pyramidal tract. Anterior sigmoid response first, at 6. C. Electrode in B elevated to new locus as indicated (adjacent histological sections). Posterior sigmoid responds first at 12.5. Calibrations 200 $\mu$V. and 5 msec.

progresses until only the radiation spike in the posterior sigmoid gyrus remains to mark thalamic activity. When this too disappears the positive spike and wave with a trace of the negative wave still persist in anterior sigmoid and may be presumed to represent true antidromic activity. This experiment also suggests that dromic activity forms a significant portion of the later phases of the anterior sigmoid response before anoxia is produced.

Since the evidence thus far presented indicates that the largely antidromic anterior sigmoid response derives from activity in the superficially placed pyramidal tract, it would be expected that a superficial stimulus at threshold intensity should activate pyramidal fibers alone. Figure 3 A shows that even at threshold for the pyramidal tract there may be sufficient current spread to stimulate the afferent pathway in the lemniscus. In other preparations (fig. 4, B) some degree of separation was seen. A distinct demonstration of current spread was obtained by recording one series of responses at increasing intensity with the stimulating electrode in the pyramid (fig. 3, B) and another series with the electrode in the lemniscus (fig. 3, C). Thus the anterior sigmoid response has lower threshold in the pyramidal tract, and the posterior sigmoid response, in the lemniscus.

The anoxia experiments indicated that there is a dromic synaptic component in the later portion of the anterior sigmoid response. Figure 4 A, an experiment with a large and variable posterior sigmoid dromic response, shows a delayed reflection of the posterior sigmoid spike complex in anterior sigmoid (cf. also fig. 3, C). The delay of more than a millisecond corresponds to the latency of anterior sigmoid response to posterior sigmoid stimulation. This apparent cortico-cortical projection seems homologous to the secondary visual projection to suprasylvian gyrus (Clare and Bishop 1954). Further evidence of this projection is the persistence of some of the anterior sigmoid positive wave after medullary section of the pyramidal tract (fig. 4, B, C; also fig. 9, V). This wave begins before and during the second major posterior sigmoid spike which is the first sign of corticofugal discharge (Bishop and Clare 1953 b). This finding suggests that there is some thalamocortical as well as cortico-cortical projection to anterior sigmoid.

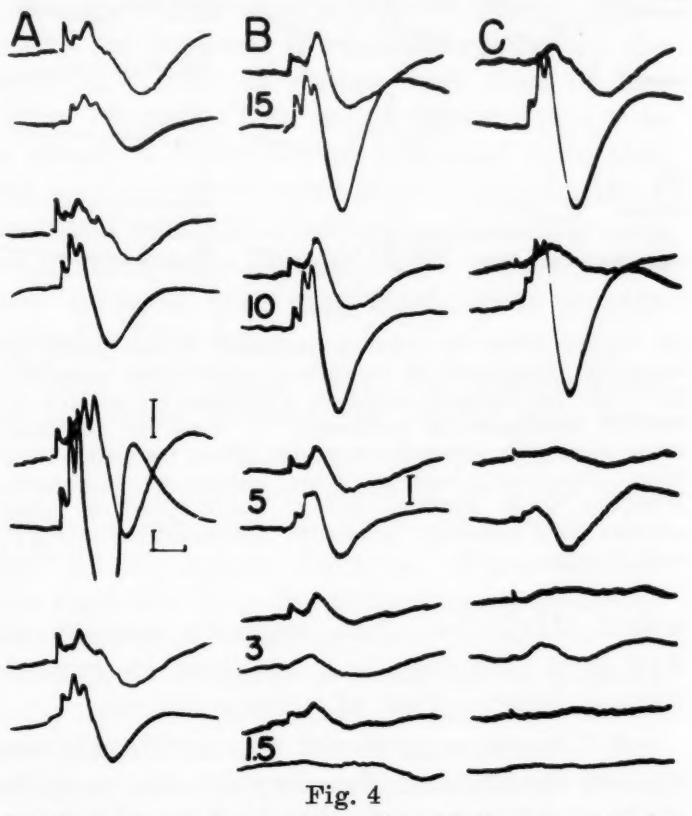


Fig. 4

A. Upper trace is anterior sigmoid, lower, posterior sigmoid. Series of responses at about 2 sec. intervals. Note that the late components of anterior sigmoid response seem to reflect the level and pattern of response in posterior sigmoid. B. Response to surface stimulation of pyramid at indicated arbitrary voltage scale values. Posterior sigmoid response first evident at 3. C. Same as B after severing pyramidal tract near the pons. Attenuated late portion of anterior sigmoid response persists. Calibrations 200 $\mu$V. and 5 msec.

The ultimate proof of the dromic nature of the posterior sigmoid potential complex is its selective removal by section of the lemniscus in the midbrain (fig. 5, A, B). This control was therefore used in all subsequent study of the antidromic response.

With variation of stimulus intensity it was shown that the fast conducted antidromic positive spike has lower threshold than the positive wave (fig 5, C). The latter appears before the spike attains half amplitude (shock duration 0.2 msec.). The negative wave increases with shock strength and may appear at intensities too low to elicit the positive wave. This pattern of the pure antidromic response suggests that the positive components

be assigned to axon-soma response in two major fiber groups, and that the negative wave be assigned to antidromic conduction up the

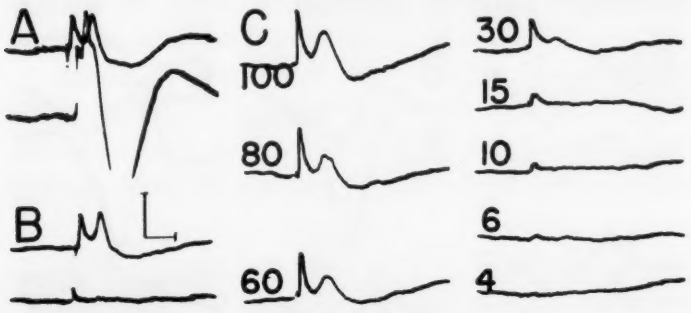


Fig. 5

A. Upper trace is anterior sigmoid, lower posterior sigmoid. Response to medullary pyramidal stimulus. B. Posterior sigmoid response abolished by section of medial lemniscus in midbrain. C. Another preparation. Anterior sigmoid response after lemniscus section. Arbitrary voltage scale values as indicated. Positive wave appears before early positive spike attains half maximal intensity. Calibrations 200 $\mu$V. and 5 msec.

apical dendrites. The negative component was most variable and sensitive to experimental deterioration of various causes.

A 2-shock sequence of the antidromic response shows some recovery of the positive spike at 0.5 msec., complete at 2.0 to 2.5 msec. (fig. 6, A-H). The positive wave is probably completely recovered by 4-6 msec. Uniformly there is a great potentiation of the negative wave with shocks close together (fig. 6, J-M). This finding supports the thesis that the negative wave is derived from apical dendrites since they are characterized by summating graded response when activated synaptically or directly (Clare and Bishop 1955 a and b).

Further analysis of the vertical locus of potential in the antidromic response (fig. 7, A-C) shows that the negative wave occurs superficial to the fifth layer of cortex and that it occurs earlier with steeper slope at deep than at superficial levels. This logically indicates slow conduction upward from the cell bodies in the apical dendrites. Unless one assumes the conditions of isolated frog nerve on a wet blotter: all or none conduction, uniform fiber diameter, and a uniform medium extending far beyond active units — none of these properties is present in cortex — no valid measurement of dendrite conduction rate in a volume conductor such as cortex can be made. That the rate is in the C fiber range, however, may be admitted.

In some experiments less prominent late oscillations were recorded at and below the cell body level. Surface negative and diphasic as well as surface positive forms were seen. These potentials were tentatively assigned to basal dendrites; it is postulated that the

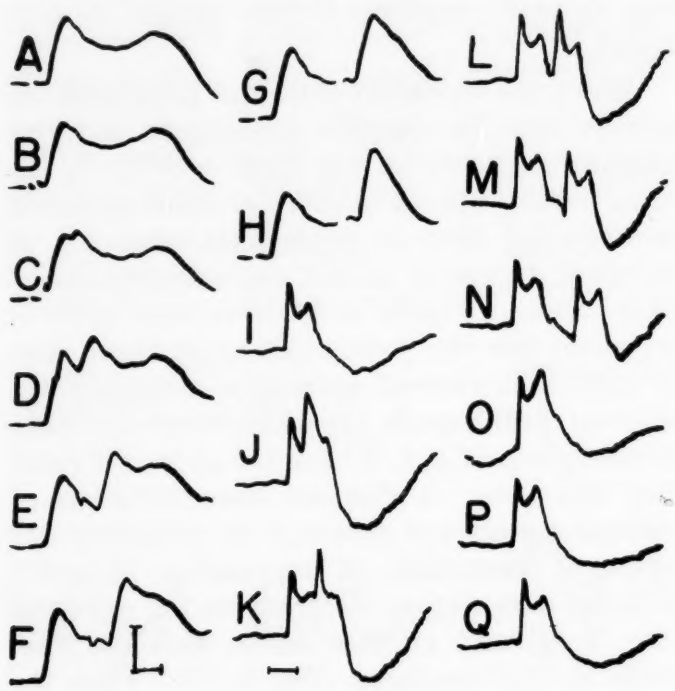


Fig. 6

Two shock sequence in anterior sigmoid after lemniscus transection. A. Single. B. 0.3 msec. interval. C. 0.5 msec. D. 1.0 msec. E. 1.5 msec. F. 2.0 msec. G. 2.5 msec. H. 3.0 msec. I. Single. J. 2 msec. K. 4 msec. L. 6 msec. M. 8 msec. N. 10 msec. O. 15 msec. P. 40 msec. Q. 100 msec. Calibrations 100 $\mu$V., 1 msec. in A-H and 5 msec. in I-Q.

electrodes were imperfectly placed to avoid recording potential gradients parallel to the cortical surface.

Figure 7, A-C also shows that the positive spike and wave are the consequence of extracellular current flow toward a sink at the fifth (Betz cell) layer; this level is negative to points both superficial and deep to it. Thus the major portion of the surface positive potentials must be assigned to soma (cell body) depolarization. In fact, the soma potentials are so large compared with those recorded beneath the cortex in the white matter, that there is some question whether the white matter potentials should be assigned to true axone potentials or spread of action currents

from the nearby discharging somata. In some experiments the potential reversal of the surface positive wave occurred slightly superficial to that of the spike; this suggests that some of the cells of origin of slower pyramidal fibers may be located superficial to the fifth layer.

Since a conduction delay between axon and soma discharge, assigned to the nonmyelinated axon segment, has been described

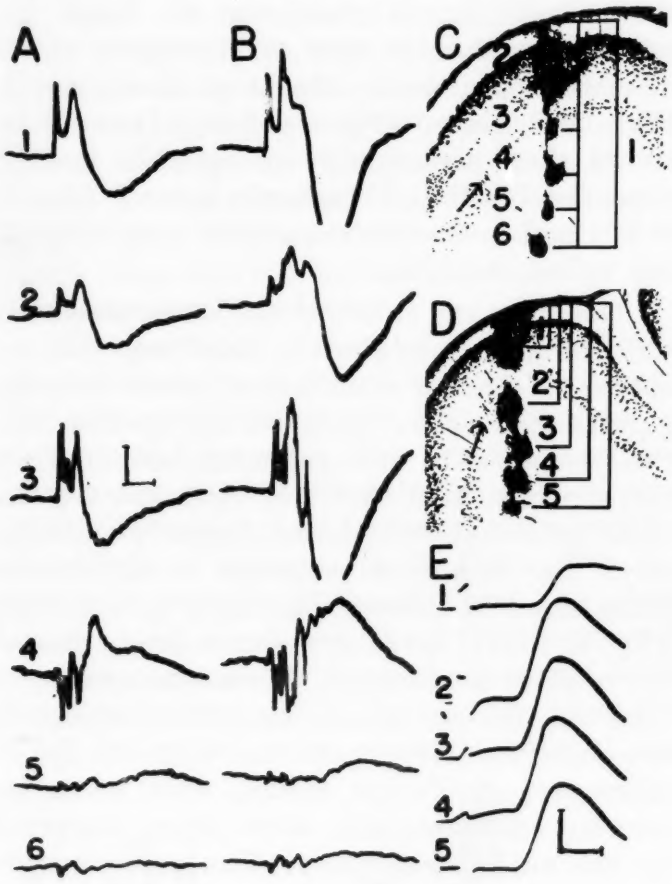


Fig. 7

A. Antidromic response in anterior sigmoid to single shocks, lemniscus cut. B. Same as A, two shocks at 2 msec. interval, to exaggerate surface negative wave. Lead 1 is from surface to white matter 2.5 mm. below. 2-6 are leads from successive 0.5 mm. segments in descending order. C. Photomicrograph showing leads for A and B. Arrow indicates cortical cell layer V. D. Photomicrograph of leads for E. E. Initial antidromic spike led between surface and successive points at 0.5 mm. intervals. Note the increased latency in the most superficial lead 1. Calibrations 100 $\mu$V.; 5 msec. in A and B; 0.5 msec. in E.

for antidromic stimulation of anterior horn cells (Lloyd 1951; Eccles 1953), the latencies of the positive spike were checked at various levels (fig. 7, D, E). The potentials were led between surface and successively deeper leads. No evidence of conduction lag below the fifth cell layer was elicited. Lacking sufficient comparative morphological information, one may guess that the cortical cell lacks a significant length of proximal unmyelinated axon.

However, there was a definite quarter millisecond lag between the spike recorded in the upper 0.5 mm. of cortex and that in the upper 1.0 mm. This lag does not appear to be simply a distortion of potential inflection due to electrotonic conduction. Alternatively one could postulate that later responding cells are situated more superficially. Indeed, it has been assumed here that most active somata are in the fifth layer.

Since the major sink for extracellular current flow during the spike has been shown to be in this soma layer, the source for recorded potential must lie in a cell component superficial to the soma, and this must be the apical dendrite. Since current flow from the deep dendrite segment precedes that from superficial segment it may be inferred that the delay is occupied by passage of the *spike* impulse into, though not at all necessarily through, the deep segment. Current flow from the superficial segment is recorded only when density is high because the sink is close by in the adjacent portion of the dendrite. This inference may be extended to indicate that the dendrite response begins immediately after the soma spike, the early negativity being masked by late arriving soma discharges of the positive wave.

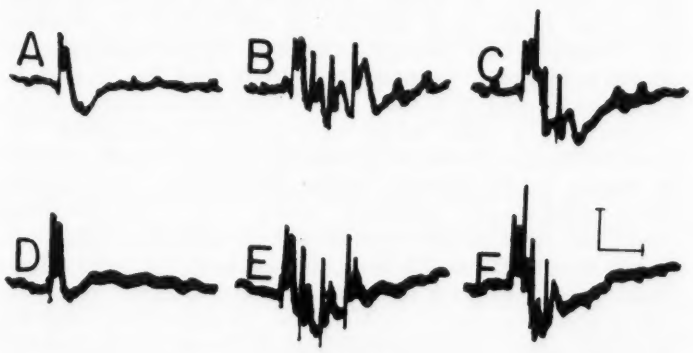


Fig. 8

DC recording of antidromic anterior sigmoid response after lemniscus section. A. Single shock. Leads surface to white matter 2.5 mm. below. B. Four shocks at 10 msec. intervals. C. Four shocks at 5 msec. intervals. D, E, and F. Same stimuli as in A, B, and C but responses are led from surface to lead at 1 mm. depth just above the Betz cell layer. Note that the superficial layers are responsible for the summating surface negativity. Calibrations 100 $\mu$V. and 25 msec.

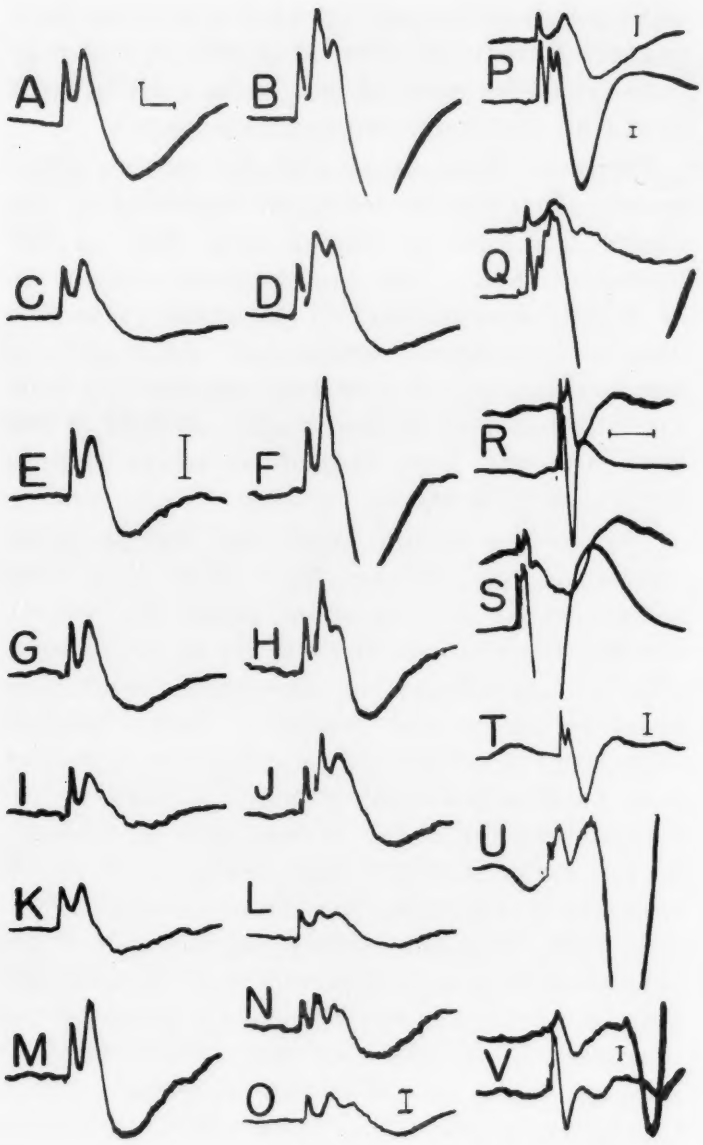


Fig. 9

Effect of drugs. A. Antidromic response after lemniscus section. B. Same, 2 shocks at 2 msec. interval. C and D. Same as A and B 4½ min. after application of veratrine. E and F. Control single and double shock antidromic responses as in A and B. G and H. Same as E and F 6 min. after strychnine application. I and J. 11 min. after strychnine application. K. Control single shock response in another preparation. L. Same as K 19 min. after strychnine application. Note additional positive wave. M. Transcortical response in another preparation without drug. N. Same position as M; lead between point just above Betz cell layer and a point 0.5 mm. below. Note the extra positive wave. O. Unusual transcortical response without drug, showing late positive wave. P. Control with intact lemniscus, upper trace anterior sigmoid, lower, posterior sigmoid. Q. Same as P 6 min. after strychninization of posterior sigmoid; driven strychnine spike. R and S. Same as P and Q at slower time base. T. Anterior sigmoid control, lemniscus intact. U. Same as T 14 min. after anterior sigmoid strychninization. Delayed driven strychnine spike. V. Anterior sigmoid above, posterior below. Same experiment as figure 4, C. Strychnine applied after pyramid section. Delayed driven strychnine spike. →

A similar mechanism appears to operate for the late arriving pyramidal impulses that give rise to the positive wave. Thus the peak of the wave is later in the highest segment of cortex than in that beneath (fig. 7, A, 2 and 3).

The summation of negative waves shown in the two shock series could be shown to persist with repetitive stimulation and DC recording (fig. 8). This apparent graded response addition is prominent at shock intervals less than 5 msec., still evident at 10 msec., and practically absent at 15 msec. (cf. Clare and Bishop 1955 a and b). It could be shown that this negative potential is located superficial to the cell bodies in layer V (fig. 8, C-E), and is therefore entirely assignable to the apical dendrites.

Goldring and O'Leary (1954) showed that strychnine exaggerates the local negative response to cortical stimulation just as it exaggerates the negative phase of the specific cortical response to afferent stimulation. They also demonstrated that veratrine will depress these potentials with some degree of specificity. The dendritic response to antidromic stimulation is, indeed, depressed by veratrine (fig. 9, A-D); there is a slight depression of the positive components. It was unexpected to find that the antidromic dendritic response is depressed by strychnine too (fig. 9, E-J).[1] Moreover, strychnine spikes, even when occurring spontaneously, were never triggered by the antidromic volley. The positive components of the antidromic response were slightly diminished always, and were transiently reduced by occlusion with the cell discharge in spontaneous strychnine spikes. Records from various levels of cortex as in figure 7 simply confirmed the drug effects with leads across the whole cortex.

In some experiments after strychnine had been active for several minutes there appeared

[1] This has also been observed independently: PURPURA and GRUNDFEST, *Nature*, **1956**, *Fed. Proc.*, **1956**; *Proc. Amer. EEG Soc.*, **1956**; *Trans. Amer. Neurol. Ass.*, **1956**; PURPURA, *Science*, **1956**.

Calibrations 5 msec. for A-Q, 25 msec. for R-V. Voltage calibrations 100 $\mu$V. in A for A-D, in E for E-N, in O for O, in P for P-S, in T for T-U, in V for V.

another positive wave following the original spike and wave (fig. 9, K, L). The simplest explanation of this change is that the extra positive wave appearing in the wake of the disappearing dendritic negative wave, represents an arrest of the dendritic response near the soma without further propagation upward. Such a hump was seen occasionally in records of the soma-dendrite segment of undrugged cortex when it was not apparent in the total cortex record (fig. 9, M, N). Another possibility is that removal of the negative wave exposes the soma potentials of a third segregated group of pyramidal tract fibers. Rarely the hump was seen in the record from undrugged full thickness cortex (fig. 9, O). Either or both theses seem more likely than more nebulous theories like that invoking axon collaterals.

The excitatory effect of strychnine with the lemniscus path intact is quite prominent. On posterior sigmoid the negative phase of the specific response was greatly increased with an increase in the duration of the initial positive phase and an increase in the number of individual spikes (fig. 9, P-S). The last effect is slightly different from the usual change in striate cortex where the exaggerated negative encroaches upon the positive without obvious increase in the number of spikes. The spikes are very probably present but swamped by the early negative potential (Bishop and Clare 1953a).

The response with strychnine in anterior sigmoid is significantly different when the lemniscus is intact. In 10 of 12 such experiments the anterior sigmoid strychnine spikes could be driven by the medullary stimulus. The spike was usually (7 animals) delayed after the shock from 20 to 50 msec., a rather constant value in each case (fig. 9, T-V). In one experiment the driven spike came early as in posterior sigmoid, and in two, there were both early and late driven responses. It is apparent that driven strychnine spikes occur only when dromically conducted impulses reach the forebrain; there is no explanation for the prolonged latency in anterior sigmoid. Similar delayed strychnine spikes may follow medial thalamic stimulation (Bishop and Clare, unpublished).

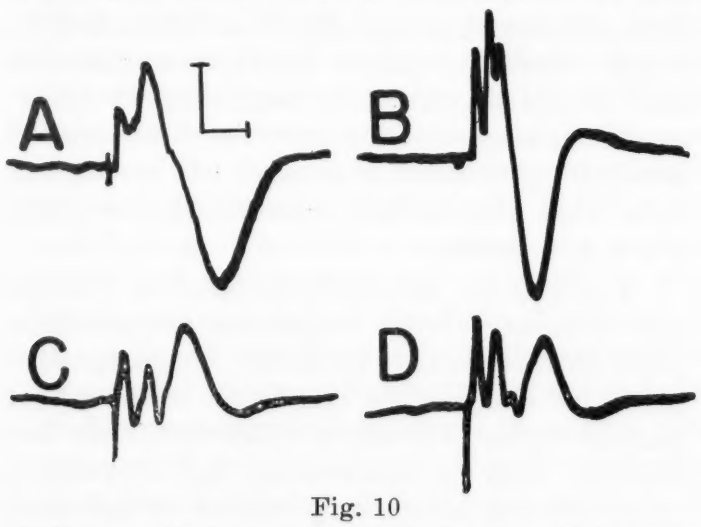


Fig. 10

A. Transcortical response in anterior sigmoid to pyramidal stimulus, lemniscus intact. B. Transcortical posterior sigmoid response to same stimulus. C and D. Same surface leads as A and B led against an indifferent lead at anterior edge of frontal sinus. Note the distortion of potential forms and the appearance of the antidromic spike in the posterior sigmoid record. Calibrations 200 $\mu$V. and 5 msec.

## DISCUSSION

It appears from this study that practically no antidromic potentials can be detected outside the Betz-cell-containing pericruciate cortex. Since it is recognized that the large axons of the pyramidal tract are derived from this area almost entirely, it should not be surprising that the small fiber (and cell) components projecting from neighboring cortex are undetectable in a volume conductor. Two factors may account for the lack of confirmation of previous workers by this study. First, this study shows that significant contamination by dromic impulses in the medial lemniscus can be avoided only by severing the brainstem except for the peduncle. Second, it is likely that serious distortion of results in the previous studies derives from the generous interpretation of potentials recorded from the convoluted frontal pole with monopolar leads. Figure 10 demonstrates this distortion with transcortical and monopolar leading from the same locus. Although the record from a transcortical lead in posterior sigmoid gyrus shows that there is no projection into it of the antidromic spike potential, the identical surface monopolar lead shows the spike at full size. The general distortion of potential form in both gyri is apparent (cf. Bishop 1950). Obviously there is no greater intrinsic validity

in one electrode circuit than another, but the analysis of monopolar recordings appears more difficult to the present author.

The importance to studies of the pyramidal tract of severing all paths from stimulus to response except the critical one was pointed out clearly by Lloyd (1941). Since the nearest major tract is the ascending lemniscus, it appears that studies of dromic descending activity in the pyramidal tract are less likely to be distorted by current spread than those under discussion. Nevertheless Lloyd's principle is obviously useful and all workers (including the present writer, 1952, 1953) have either ignored it entirely, or have not used the control in all experiments.

It is of some interest that in the case of antidromic activation of cortical pyramids where the anatomical substrate is relatively certain, there is a surface positive spike assignable to soma and proximal apical dendrite discharge, followed by a slow negative assignable to upward dendritic conduction. This is in a sense a confirmation of a similar mechanism assigned to the potential components of the specific response in optic cortex (Bishop and Clare 1952, 1953a). In the optic cortex it was inferred that synaptic terminals fire the cell body first. A slow positive-negative complex then signals propagation up the dendrites. In the antidromic response the slow positive phase of this complex is not obvious, although it could constitute a portion of the positive potentials assigned chiefly to soma response. The graded response character of apical dendrites inferred from the results with direct and trans-synaptic dendritic stimulation (Clare and Bishop 1955a and b) is well confirmed by this study.

There are several differences between antidromic response in cortical pyramidal cell and that in anterior horn cell. Where the cortical spike has completely recovered 2 msec. after discharge, the spinal cell body begins to recover at about 1.7 msec. and is completely recovered in 4 msec. (Lloyd 1951). This, together with the absence of evidence for axon-soma delay in pyramidal cell suggests that its faster recovery may depend less upon a different responsiveness of soma membrane than upon the lack of a low "safety factor" in the non-myelinated segment of axon.

The potential assigned to dendrites also differs in the two types of cells; the spinal dendritic potential is only slightly longer than that assigned to axons, does not summate with repetition, and has a prolonged 120 msec. depression after discharge. Although the 15-20 msec. dendritic potential of cortical neurons may partially result from conduction over a longer distance, this does not appear to be an adequate explanation for the difference. Moreover the cortical dendrite can summate its discharges with repetitive volleys, but lacks any distinct post-stimulatory depression.

When dendritic response was produced by synaptic or direct excitation, Clare and Bishop (1956) did observe a period of post-excitatory depression in apical dendrites of optic cortex. It may be that this is not apparent with antidromic stimulation because the impulse is directed "downhill" into a small membrane area and more favorable "safety factor". Also the membrane depolarization here may be less nearly complete.

In any case there are unexplained differences between pyramidal and spinal motor cell which suggest that the morphological distinction of dendrites does not necessarily correlate with uniform functional properties. The recent study of the crustacean soma-dendrite (Eyzaguirre and Kuffler 1955a and b; Kuffler and Eyzaguirre 1955) states that the same dendritic structure may support all-or-none impulses in one portion and graded generator potentials in another. It is not even clear that the border between the response types is a constant one.

There is no adequate explanation for the fact that strychnine depresses the dendrite fired antidromically, since the drug augments potential assigned to dendrites in direct or transsynaptic activation. However, this fact together with the observation that strychnine spike driving occurs only via an orthodromic pathway does suggest that the drug operates primarily on the synaptic mechanism rather than upon the neural membrane as a whole. If one postulated that the drug has a prostigmine-like effect at dendritic synapses, one might infer increased responsiveness to a

synchronized transient synaptic volley as well as some sustained depolarization after-discharge to account for depression of antidromic response. The fact that strychnine augments the response to local cortical stimulation would then require the *ad hoc* hypothesis that the local shock activates dendrites via presynaptic elements. Such helpless speculation may serve to emphasize the need for evaluation of drug effects with intracellular recordings.

Allowing for species differences there is some degree of correlation between the results in the cat and those recently reported in the rabbit (Chang 1955a and b). There are questionable features of his conclusions, however, particularly those which are elaborated into a thesis of synaptic activation by axon collaterals. It appears to the present author that such results are more parsimoniously assigned to uncontrolled current spread to the medial lemniscus which sets up a pattern of afferent specific response in rabbit cortex that has been well known for some time (Bartley 1933; Bartley and Bishop 1933a and b; Bishop 1933).

## SUMMARY

The cortical response to medullary pyramidal tract stimulation in the cat has been recorded with vertically oriented bipolar electrodes. The true response uncontaminated by the dromic response due to current spread to the medullary medial lemniscus was obtained by lemniscus section in the midbrain. The antidromic potential is practically confined to the Betz cell containing area about the cruciate sulcus, particularly anterior sigmoid gyrus. The pattern consists of a positive spike and wave which are assigned to soma and proximal apical dendrite discharge in the cells of origin of two major groups of pyramidal fibers. Following and probably underlying the positive wave is a slow negative wave assigned to antidromic conduction in apical dendrites of both cell groups. No axon-soma delay was recorded.

When the lemniscus is intact there is a prominent specific response in posterior sigmoid with delayed cortico-cortical and possibly thalamo-cortical projection to anterior sigmoid. Strychnine spike driving in both sigmoid gyri is possible only when the afferent path is functioning. The lemniscus specific response has a prolonged but incomplete depression phase in its excitability cycle, assigned largely to the thalamic relay.

The true antidromic response has a rapid recovery after-discharge. At short intervals there is prominent summation of the negative wave; this is inferred to be further evidence for the graded response character of apical dendrites. With repetitive stimulation this summation can maintain a DC potential shift.

The most prominent effect of both strychnine and veratrine on the antidromic response is to depress the dendritic potential.

Miss M. H. Clare, Mr. C. P. Robertson, and Mrs. M. Eager assisted with these experiments at various times.

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# A NOTE ON THE CHARACTERISTIC RESPONSE PATTERN IN PRIMARY SENSORY PROJECTION CORTEX OF THE CAT FOLLOWING A SYNCHRONOUS AFFERENT VOLLEY [1]

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It is well-known that the complex pattern of response to optic nerve shocks in visual cortex of the cat is distinctly different from the simpler and more variable diphasic response to relatively asynchronous photic stimulation (Bishop and O'Leary 1938; Marshall, Talbot and Ades 1943). However arbitrary the synchronous volley, it is scarcely more arbitrary than any other transient, and it has served as a productive tool in the analysis of cortical physiological connections. Perhaps because this pattern was not seen in somatosensory and auditory cortex even with electrical stimulation of sensory nerves and end organs (Marshall, Woolsey and Bard 1941; Woolsey and Walzl 1952), a special organization of visual cortex may have been inferred, explicitly or otherwise. The well-known distinct morphological character of striate visual cortex served to support this view.

It is obviously unfair to compare the cortical response to immediately prethalamic stimulation of the optic nerve with the response in other sensory systems to stimulation at sites removed from the thalamus by one or more synapses. Many workers have recognized this and Marshall (personal communication) found no difference between the response of visual cortex and that in the somatosensory cortex with internal capsule stimulation. A polyspike positive phase of the response of somatosensory cortex to relay nucleus stimulation was described by Dempsey and Morison (1943), and similar records were recently published by Perl and Whitlock (1955). A suggestively similar response to stimulation of the medial geniculate nucleus was recently shown by Bremer and Terzuolo (1955).

Nevertheless the homologue of the visual cortex response in somatosensory cortex was interpreted as an antidromic pyramidal tract response (cf. Porter 1955), and the response of visual cortex to optic nerve shock was elaborately endowed with the mechanism for color vision (Chang 1950, 1952; Chang and Kaada 1950; for other views cf. also Bishop and Clare 1951, 1952, 1953a and b; Clare and Bishop 1952). The cat was subsequently shown to be color blind (Meyer, Miles and Ratoosh 1954).

The present study demonstrates that synchronized afferent volleys in the projection pathway of any of the three major sensory systems will elicit highly similar and characteristic responses. Evidence is also presented to show that such responses in visual cortex cannot be duplicated by activation of the corpus callosum (cf. Bremer, 1955a and b).

## METHODS

Adult cats were anesthetized lightly with Surital (thiamylal sodium). Deep stimulating electrodes were 3 needles or wires about 1 mm. apart. On the surface 3 silver wires 1 mm. apart were applied; 0.05 msec. square waves were usually used through the circuit described previously (Landau 1956). Electrode placements were checked by Marshall's technique (1940). Unless specifically indicated, all responses were routinely recorded between 75 $\mu$ steel wires, one on the surface and one 2 mm. below in the subcortical white matter.

[1] This work was supported in part by United States Public Health Service grant B-882 and by a grant from the Supreme Council Thirty-Third Degree Scottish Rite, Northern Jurisdiction, U.S.A., through the National Association for Mental Health.

For monopolar recording the indifferent lead was placed over the frontal sinus near the midline.

## RESULTS

Deep stimulating electrode positions were within the appropriate relay nucleus, ventralis posterior, medial geniculate, or lateral geniculate. Responses were best recorded in the posterolateral portion of posterior sigmoid gyrus, the superior portion of the anterior flexure of ectosylvian gyrus, and the mid portion of lateral gyrus. No attempt was made to map the margins of these responses; a few responses of lower amplitude, simpler form and the same or longer latency were recorded surrounding the loci that were studied in detail.

Figure 1 shows similar responses in the three sensory areas of the same cat. All have latencies of 0.3-0.4 msec. Following the first spike, assigned to radiation axon terminations, there is a series of 3 spikes at approximate intervals of 1.4 msec. (the last may be seen only as an inflection on the ensuing negative wave). These spikes have been assigned to serial and possibly repetitive response in groups of pyramidal cells. Between the first radiation spike and the next major spike there is a minor spike which is evident to varying degree in different loci (fig. 1, D, E, F) (Marshall, Talbot and Ades 1943). In visual cortex this has been assigned to a short axon cell discharge (Bishop and Clare 1951, 1953b).

In all three areas the cortical response retains the basic patttern as the stimulus intensity is decreased (fig. 1, A, B, C). At minimal intensities no inflections after the second major spike may be apparent. The lower trace in figure 1 F is a visual response in another cat, exceptional because of the slightly decreased interval between major spikes. This represents the observed range of temporal variation of this pattern.

The patterns of figure 1 can also be elicited by synchronous activation of the tracts afferent to the relay nuclei. In these experiments displacement of the stimulating electrodes a few millimeters into medial lemniscus, lateral lemniscus, or optic tract produced a discontinuous increase of latency of about 0.7 msec., time for one synapse. The simultaneous activation of pre- and postsynaptic elements could be a significant technical problem. This difficulty was met by moving the stimulus leads toward the particular nuclear radiation pathway until the lowest threshold response lacked the synaptic delay.

The prethalamic path can be stimulated satisfactorily more distally in the optic nerve, or in the medullary medial lemniscus and dorsal column nuclei (Landau 1956; Perl and Whitlock 1955). A few attempts to stimulate the auditory path at the trapezoid body elicited only a simple diphasic wave like that produced by cochlear stimulation (Woolsey and Walzl 1942). Thus it appears that desyn-

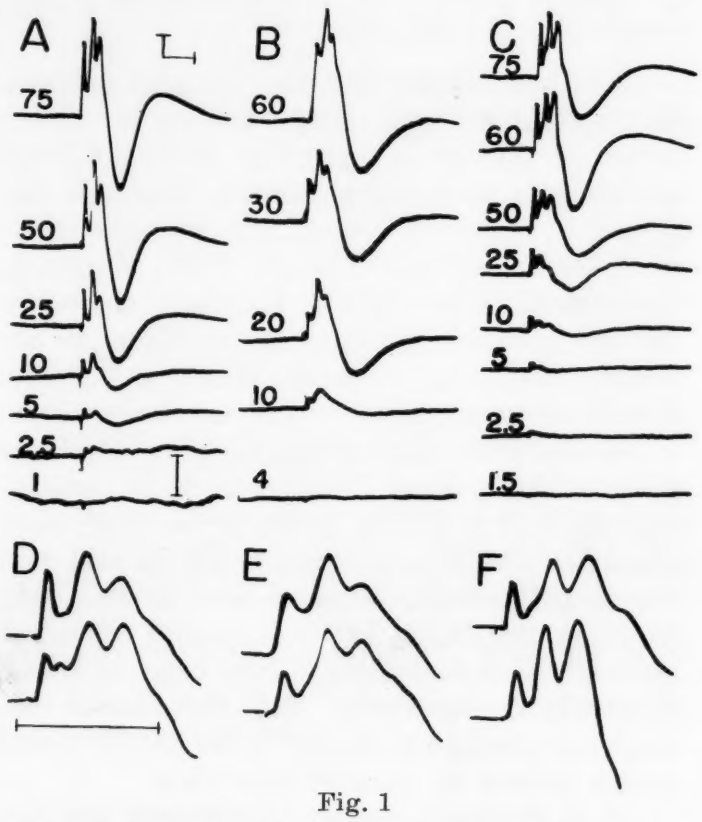


Fig. 1

Transcortical recording of responses of projection cortex to stimulation of specific relay nuclei of thalamus. A. Somatosensory cortex, effect of reducing shock intensity, arbitrary voltage scale. B. Auditory cortex, series as in A. C. Visual cortex, series as in A. A, B, and C are from the same preparation. D. Upper trace is same as A at faster time base. Lower trace is from a nearby point where the small spike is more prominent. E. Upper trace is same as B at faster time base. Lower, at adjacent point, shows a suggestion of the minor second spike inflection. F. Upper trace is same as C at faster time base, note the early second spike inflection. Lower trace from another cat's visual cortex; spike intervals are slightly shorter. Calibration, 5 msec. and 200 $\mu$V. Bottom two traces in A are at higher gain, calibration 100 $\mu$V. Surface lead positive up in all records.

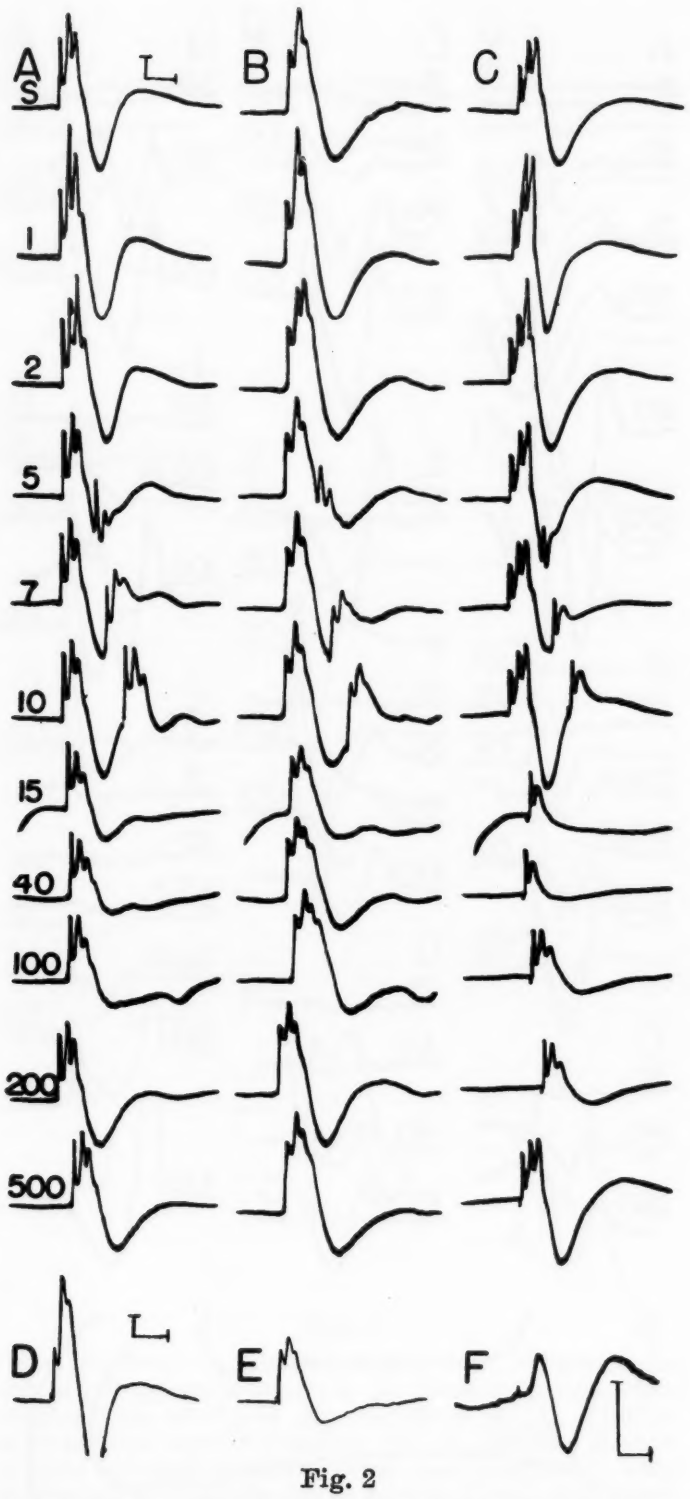


**Fig. 2**

A, B, and C are respectively somatosensory, auditory, and visual cortex, same experiment as figure 1. Upper trace is response to single shock. Subsequent traces show response to second shock at indicated delays in milliseconds. Stimulus cycle about 1.2 sec. D. Auditory cortex response in another experiment. E. Same as D after application of isotonic KC1; note depression of all but the first positive spike, and of the negative wave. F. Visual cortex of another preparation, response to callosal activation from contralateral homologous cortex. Compare with C. Calibrations 5 msec. and 200 $\mu$V. in A for A, B, and C; in D for D and E; and in F for F.

chronization of afferent volleys at prethalamic relays accounts for the obscuration of the pattern described here.

Figure 2, A, B, C shows a two shock series from the same experiment as figure 1. It is presumed that such a series demonstrates the intracortical excitability cycle since the cortical afferent neurons are excited directly. Accordingly the first cortical spike, which represents radiation fiber terminals is completely recovered by 5 to 7 msec. There is a significant degree of recovery as early as 1 msec., but accurate measurement is practically impossible where the spike components from the two shocks overlap.

Not only is the radiation spike partially recovered by 1-2 msec. but some intracortical response occurs. This is shown by the accentuated late spike inflections in the records at 1 and 2 msec. latency, and by the overall increase in amplitude of the entire positive-negative complex. There is obvious depression of the cortical response long outlasting the recovery of the radiation spike; the depression may be less deep during the early phase (Clare and Bishop 1952). Complete recovery requires from 200 to 500 msec., the negative (dendritic) wave recovering last. No special significance is attached to the greater delay in recovery of visual cortex in this experiment. The anesthetic depth may have been somewhat deeper for this series; besides, equivalent saturation of cortical afferents in each relay nucleus can scarcely be assumed.

In support of the interpretation of spike potentials implicitly derived from the analysis of visual cortex; figure 2, D, E shows in auditory cortex how isotonic KC1 may depress all potential components assigned to intracortical elements with sparing of the radiation spike (cf. figure 2, Bs and B15).

A careful re-examination of the callosal response in visual cortex (fig. 2, F) was occasioned by Bremer's recent report (1955a and b). Using monopolar recording he described responses to stimulation of symmetrical loci of contralateral cortex. These potential patterns are said to be identical with the response to optic nerve stimulation. His figures (the same in both papers) showd some spike complexes

of different time relations and polarity for which he gives no accounting.

Figure 3 illustrates our results with cortical stimulation. Confirming Curtis (1940) we found a relatively low threshold response with a latency of about 2.5 msec. quite localized to symmetrical contralateral cortical surface. The responses in lateral gyrus are smaller, less reliable, and of higher threshold than those in suprasylvian gyrus (fig. 3, A, F). With much higher intensity shocks a shorter latency response supervenes following stimulation in either gyrus.[1]

The latter response is not anatomically localized and can be obtained at similar threshold all over the convexity (fig. 3, B-E, G-I). With contralateral stimulation the positive spikes vary in prominence, but may resemble the afferent pattern. With stimulation of ipsilateral striate cortex the resemblance to the response to optic afferent stimulation is obvious (fig. 3, D, E, H, I).

The lack of anatomical specificity suggests that these responses are an artifact of current

[1] Since artifact balance is to some extent arbitrary it can be said only that the latency is no more than a fraction of a millisecond.

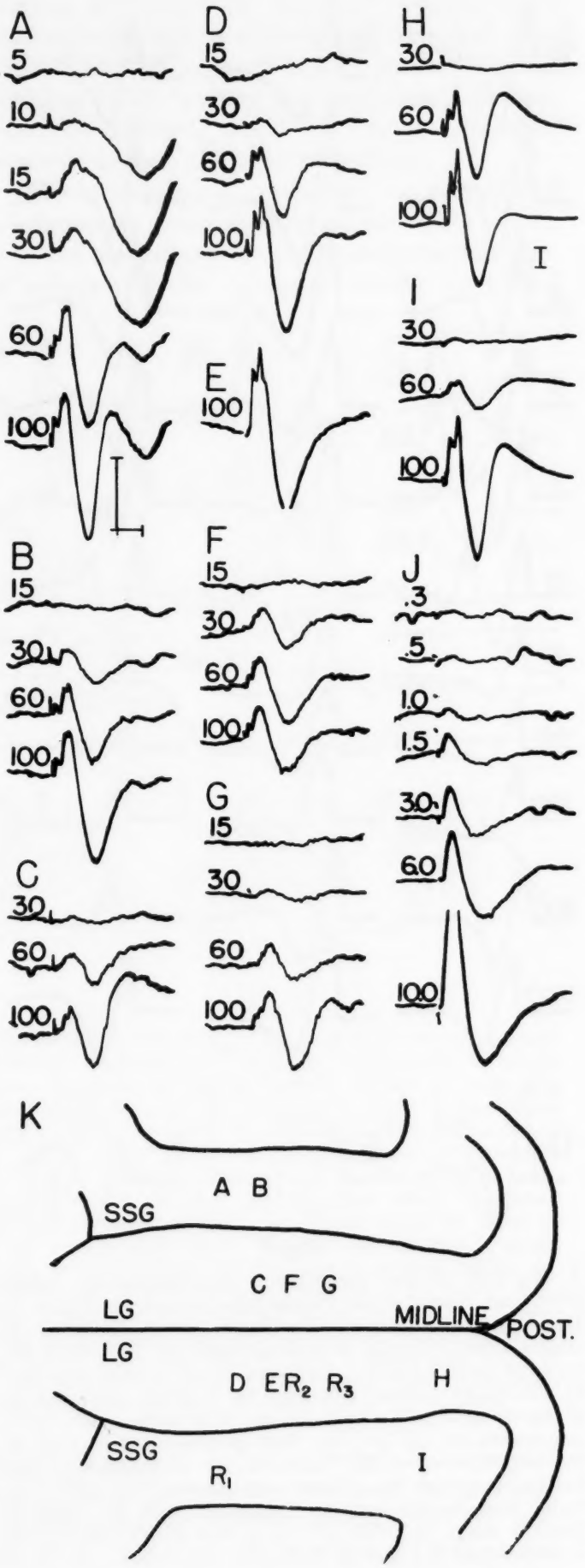


Fig. 3

Responses to cortical stimulation. Numbers indicate voltage input to 4X step-up isolation transformer, 0.05 msec. pulses. Diagram indicates electrode positions. A-E are recorded from $R_1$; F-I, from $R_2$ in the same preparation; J, from $R_3$. A. Stimulation of symmetrical contralateral site on suprasylvian gyrus. Long latency response at 10; short latency pattern appears at 60. B. Stimulus moved 2 mm. posterior to position in A; threshold for long latency response rises. C. Contralateral lateral gyrus stimulus. High threshold short latency response only. D. Ipsilateral lateral gyrus stimulus. Short latency polyspike response. E. Stimulus 2 mm. posterior to that in D; similar response. F. Stimulation of symmetrical contralateral site on lateral gyrus. Long latency response at 30; short latency appears at 60. G. Stimulus moved 2 mm. posterior to that in F. Threshold for both late and early response rises. H. Stimulus moved to ipsilateral gyrus about same distance (8-9 mm.) from $R_2$ as F. High threshold short latency polyspike response of high amplitude. I. Stimulus 8-9 mm. from $R_2$ on striate portion of suprasylvian gyrus. Response similar to H. J. Another animal. Direct stimulation of midline corpus callosum with 0.5 msec. pulses; recorded from striate cortex at $R_3$. Simple delayed diphasic potential at all intensities. K. Diagram of dorsal surface of cat brain; letters indicate recording and stimulating sites. SSG — suprasylvian gyrus. LG — lateral gyrus. Calibrations 200 $\mu$V. and 5 msec.; lower gain as indicated in H and I.

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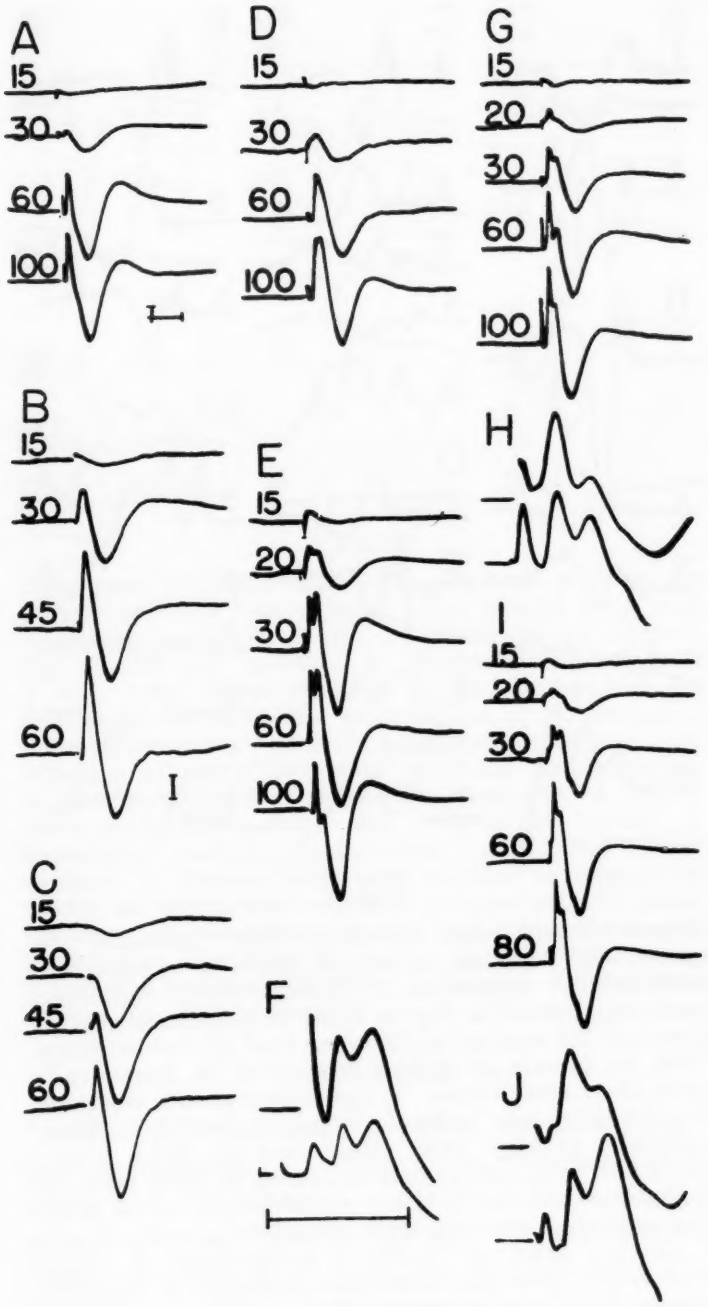


Fig. 4

Local response to cortical stimulation. Numbers indicate voltage as in figure 3. A. Stimulus 1 mm. from suprasylvian electrode $R_1$ in figure 3. B. Similar suprasylvian locus in another cat. C. Same as B with current reversed; positive phase less prominent. This difference is probably due in part to actual difference in the stimulated field of tissue as well as to the electrical artifact. D. Suprasylvian response in still another preparation. E. Lateral gyrus response to stimulus about 1 mm. away. Electrode placement $R_2$ in figure 3. Note the encroachment of the negative wave upon the positive spikes. F. Upper trace is the same as E at a faster time base; compare with lower trace response to optic tract shock in the same cat. G. Lateral gyrus in another cat. H. Upper trace same as G; compare with optic radiation shock in same cat. I. Lateral gyrus in still another cat. J. Upper trace same as I; compare with optic radiation response in same cat. Calibrations 5 msec. and 200 $\mu$V. Higher gain in B and C as indicated.

spread. It would still be conceivable that larger shocks are required to reach a rapid conducting callosal system which might lie deeper in the cortex than the elements mediating the slow response. If stimulated directly such a fast conducting system would, of course, have a lower threshold than the smaller slower fibers. Direct stimulation of the corpus callosum, however, elicits in lateral gyrus only the slower simple diphasic response described by Curtis (fig. 3, J).

More information is needed to explain Bremer's results. If his records are the result of current spread, then it must be shown that the local response to cortical stimulation does have some features of the afferent response. Figure 4, E-J shows that in lateral gyrus this is indeed the case (note that the amplification is about ⅛ that in figure 3). It appears that the threshold of the deeplying cortical afferents is sufficiently low so that they initiate a cortical response at intensities too low to activate cortical elements directly. The fact that we used short shocks and relatively widely spaced stimulus leads seems to account for the difference from the results of Bishop and Clare (1953a). Using closely spaced stimulus leads at or near the cortical surface they obtained only the surface negative dendritic response. It is, of course, probable that some direct cortical stimulation occurs in the present experiments; the dendritic response with larger shocks tends to engulf the positive spikes (fig. 4, E). Moreover there is minor variation of the spike latencies from those seen in true afferent responses (fig. 4F, H, J).

Furthermore it was found that the positive spike sequence is obscure, if present at all when stimuli are applied to suprasylvian association cortex (fig. 4, A-D). This difference from visual cortex was also noted with subcortical stimulation (Bishop and Clare 1953a). It appears therefore, that association cortex lacks the type of rapidly conducting low threshold afferent system found in sensory projection cortex.

In order to simulate Bremer's records entirely it was necessary to employ monopolar lead combinations (fig. 5, A). Here it is shown that the high threshold short latency response

derived with transcortical leads and assigned to pickup from the opposite hemisphere, becomes a prominent spike complex with monopolar leads.

A more convenient way to analyse the distortion due to monopolar leads was to activate one cortex synchronously by means of an afferent volley in the optic tract or radiation (fig. 5, B-F). Thus in some experiments (fig. 5, B, F) it could be shown that spikes in the hemisphere opposite that activated by the afferent volley occur only with monopolar leading (note the eightfold difference in gain on the two sides). Moreover, there is no simple relationship between the spikes in the ipsilateral cortex and those in the contralateral monopolar leads. Some of the early deflections in the monopolar leads must, in fact, represent subcortical components of the optic system. When the ipsilateral response is largest, early spike components may appear contralaterally even in the transcortical leads (fig. 5 C-E). These spikes assigned to current spread do not vary in correspondence with the latency of the ipsilateral response. In contrast the delayed positive-negative wave does so vary and is assigned to true callosal response to relayed afferent volley.

Bremer states that acute callosal transection abolishes the "callosal" responses he describes in lateral gyrus. Kempinsky (1956) has shown that visual cortex is depressed by such a procedure; we confirmed this in one acute experiment and found that midline edema and bleeding were significant difficulties. When the experiment was done several weeks after the callosal section (fig. 6) the spurious callosal response was well demonstrated with monopolar leading from cortical surface symmetrically contralateral to the stimulus. This pattern is obviously field potential spread from the stimulated side rather than local activity since the response is not significantly changed by leading at intra- and subcortical points. We have not been able to account for the long interval (about 2.5 msec.) between the major spikes (1, 3 and 4) in Bremer's responses to optic nerve stimulation.

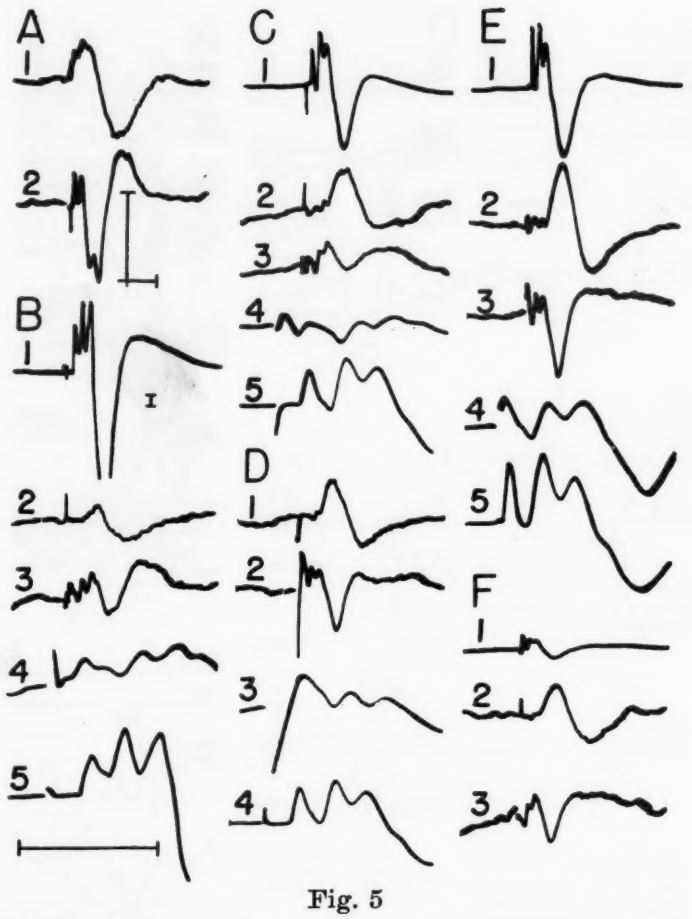


Fig. 5

Effect of monopolar recording upon "callosal" response. A. Response in lateral gyrus to symmetrical contralateral stimulus. 1. Transcortical recording, same experiment as figure 3, F, 100. 2. Same surface electrode led against indifferent lead at frontal sinus. Note the prominent spike components. B. Response to optic tract stimulation. 1. Ipsilateral striate response. 2. Contralateral callosal response recorded transcortically at high gain. Note lack of spike components and long latency corresponding to relay from the ipsilateral cortex. 3. Same surface lead as in 2 led monopolarly; specious spike complex appears. 4 and 5 are the same as 3 and 1 respectively at faster time base. Note the non-correspondence of spike latencies. C. Another preparation, records arranged as in B. In C2 a trace of the ipsilateral spike pattern can be seen even with transcortical recording. D. Same experiment as C; different stimulus lead cathodal at 1/3 less intensity than in C. 1. Contralateral response recorded transcortically, trace of the early spike pattern. 2. Exaggeration of spikes with monopolar lead. 3. Faster sweep of 2 compared with ipsilateral response in 4. E. Same experiment as C; stimulus raised to optic radiation. Records arranged as in B and C. Note in E2 that the true callosal response, the positive-negative wave, is earlier than in C2, corresponding to the geniculate relay time in C. The spurious spike potentials in C and E are not demonstrably correlated. F. Same experiment as E with lower shock intensity. 1. Reduced ipsilateral response to radiation shock. 2. Contralateral response without significant spike components in transcortical recording. 3. Monopolar lead from same point as 2; spikes again present. Calibrations 5 msec. and 200 $\mu$V. Low gain calibration applies to all ipsilateral records; high gain, to all contralateral ones.

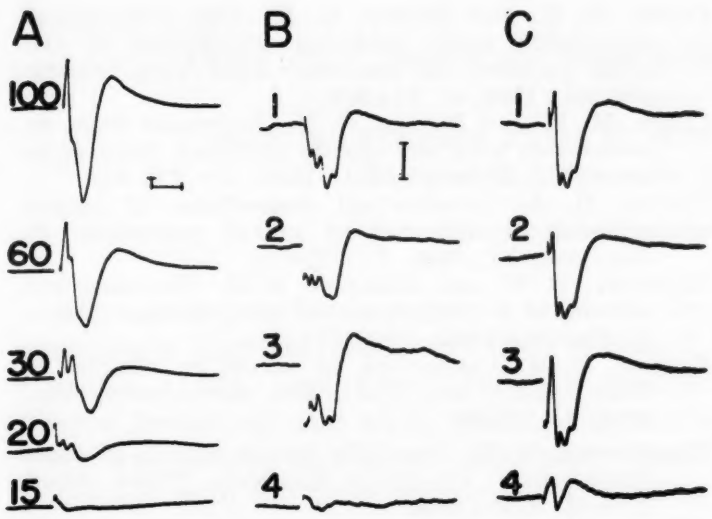


Fig. 6

Responses 23 days after the posterior 3/5 of the corpus callosum was severed. The lateral gyri were separated by about 2 mm. of postoperative thickening of the falx cerebri. A. Transcortical responses 1 mm. away from stimulus on the mid-portion of lateral gyrus, intensities as in figure 4. B. Responses from symmetrical contralateral striate cortex, with stimulus intensity 100, note increased amplification. 1. Monopolar lead from surface electrode. 2. Monopolar lead from point 1 mm. deep within cortex. 3. Monopolar lead from subcortical point 2 mm. below surface. 4. Transcortical lead, surface to subcortical point; no significant response is apparent. C. Stimulating and recording leads both moved 6 mm. posteriorly. Records as in b. Shock artifact was readjusted between recording of 3 and 4. Calibrations 5 msec. and 200 microvolts.

## DISCUSSION

Our experiments show that the spike complexes assigned by Bremer to callosal pathways are reasonably explained as a misinterpretation of current spread. To our knowledge no tract other than the three major afferent trunks has been reported to elicit such patterns.

The obvious identity of the afferent response in all three projection areas is a *prima facie* case for similar mechanisms. Minor variations in the relative amplitude of components or in the time of onset of the negative wave are no greater between different projection areas than between different portions of the same area. It is therefore probable that data derived from the analysis of visual cortex (Bishop and Clare 1951, 1952, 1953a and b) can be transferred to other projection areas with little modification.

The fact that the spike complex could not be elicited by direct stimulation of association cortex seems to indicate not only that the specific afferents activate a special pattern of cortical activity, but also that this pattern is limited to cortex that has a specific afferent projection.

This leads to some teleological speculation. If it be granted that these direct projection systems do share the special characteristics of fastest axonal conduction, monosynaptic thalamic relay, and predominant intracortical synapse with cell bodies, it remains to explain what functional value these qualities may have.

A first consideration may be the fact of rapid conduction. Gasser (1934) gave a classifical illustration of the value of different conduction rates in the several fiber groups of peripheral nerve: it might be useful for the organism to know its toe was stubbed a few milliseconds before it started to hurt. In the meshwork of central pathways it becomes difficult to imagine how such millisecond latency differences can be of major significance.

In the phylogenetic development of the visual and somatosensory systems it appears that the more recently acquired faster pathways short circuit the persistent older connections (Bishop and Clare 1955; Bishop, personal communication). Thus it may be that rapid conduction *per se* is only a secondary property of systems whose essential quality is widespread, variable, direct, and potent synaptic connection at a distance. Such a viewpoint might also explain such neurological curiosities as the fact that a potent and exemplary short circuit pathway, the corticospinal tract, is largely constituted of slow conducting fibers.

## SUMMARY

Electrical stimulation of the thalamic relay nuclei (ventralis posterior, medial geniculate, lateral geniculate) or their immediate prethalamic projection tracts, elicits in the appropriate sensory cortices a characteristic polyspike positive and negative wave. This response may also be elicited by direct cortical stimulation in striate cortex, but not in suprasylvian association cortex. The polyspike patterns are not elicited via the corpus

callosum or other pathways. The cortical excitability cycle and the variation with stimulus intensity are described for these responses. Their mechanisms and nature are discussed.

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# CRITICAL FLICKER FREQUENCY AND CORTICAL ALPHA

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The purpose of this paper is to check the startlingly high correlation (0.855) which C. Chyatte (1954) has found between critical flicker frequency and alpha index. Chyatte's work was carried out in our laboratory three years ago with the same equipment as used in this study and in a previous one by F. P. Friedl (1954). It was on the basis of this latter study that we became uneasy about Chyatte's correlation, which is certainly the highest yet reported between measures of cortical alpha and any other variable. The same correlation attained the very inconspicuous value of 0.14 in Friedl's subsequent investigation.

Both Chyatte and Friedl used a Strobotac Model 631 B with a cardboard shield reducing the illuminated area to a circular field of 2.5 cm. in diameter. By means of a translucent piece of bond paper the illumination of this area was kept uniform at about 0.5 foot candles at the source. The same procedure was followed in the present investigation. In all three studies CFF was measured under conditions of light adaptation (LA). For our subjects, however, CFF measures after 15 min. of dark adaptation (DA) are also available. The measure of cortical potentials was obtained on the Grass electroencephalograph (Model III B) from two ½ min. records, with a 15 sec. interval between recordings during which the subjects were asked to open their eyes and again make themselves comfortable. The actual records were obtained, of course, while the subjects kept their eyes closed and tried to relax as much as possible. Monopolar recordings (occipital to ear lobe) were used. The alpha index is the per cent time during which the regular alpha pattern persists in a given record.

The subjects of this study were 56 normal, male college students whose ages ranged from 19 to 22 years. They were drawn from a larger population in such a manner as to over-represent the two extremes on the Taylor's (1953) Scale of Manifest Anxiety. It was hypothesized that the divergence between the correlations obtained by Chyatte, on the one hand, and by Friedl, on the other, could be due to the anxiety variable which was not included in the former study.

Table I gives the comparable results of the three studies. A significant difference (at the .05 level) was found between the mean CFF values of this study and those of Chyatte's ($t = 2.19$). The difference in the mean alpha indices reported by Chyatte and by Friedl is also significant at the .05 level ($t = 2.34$). We do not feel, however, that these minor discrepancies can account for the very impressive difference between the respective correlations. Our own result agrees with that of Friedl almost completely and stands in marked contrast to Chyatte's. Snedecor's (1946) Chi square test for correlation coefficients yields a value of 42.27 for 2 df which is significant beyond the .001 level.

Our hypothesis that the difference between Chyatte's very high correlation and Friedl's very low correlation might be due to differences in anxiety-proneness between the two samples was not substantiated. For 24 cases with low Taylor-scores (0-8), the correlation between CFF and alpha index was 0.07; for 26 cases with high Taylor-scores (13-39) it amounted to —0.02. These two values are neither significantly different from each other nor from zero. Therefore, we find ourselves unable to account for the huge difference between Chyatte's result and that obtained in the two subsequent studies.

It is true that Chyatte's subjects were, on the average, older (mean = 26.6 years) than ours (mean = 20.8 years; $t = 6.82$) but they were not significantly older than Friedl's subjects (mean = 25.2 years; $t = 1.40$).

Hence, it would seem that age differences can also be ruled out as an explanation. The over-representation of extreme Taylor-scores in our sample also fails to offer any cue since Friedl used a sample which represented the whole range of the Taylor scale, and since Chyatte himself has not included this variable.

As always, the possibility remains that the lack of a correlation simply may be due to the unreliability of the measures used. Unfortunately, none of the three studies provides the respective coefficients of reliability. We can obtain some estimates indirectly, however. The CFF measures taken under dark adaptation correlate with those taken under light adaptation to the extent of 0.84 and this may serve as a lower estimate of the respective reliabilities. In the case of the alpha index, we have to argue that our distribution agrees very well with that obtained by Friedl and that it is also not significantly different from Chyatte's.

This is admittedly a poor substitute for a reliability measure. But, as things stand, we do not think that reliability differences suffice to account for the difference between the correlation coefficients under consideration.

Thus we arrive at the conclusion that some factor which has so far escaped identification must have caused a spuriously high correlation between critical flicker frequency and alpha index in Chyatte's investigation. The correlation between these two variables as ascertained in two subsequent research projects is barely significant. This is a rather unhappy result because Chyatte's finding seemed very promising (Landis 1953) particularly in regard to his factor of "central readiness". However, this factor rests primarily upon the high correlation between CFF and alpha index. With this correlation reduced below significance the reality of the factor appears rather doubtful.

TABLE I

MEANS AND STANDARD DEVIATIONS OF VARIABLES AND THE CORRELATIONS BETWEEN THEM IN THREE STUDIES

| *Author* | *n* | *CFF (per min.)* | | *Alpha Index* | | *Correlation CFF: Alpha Index* |
|---|---|---|---|---|---|---|
| | | *M* | *SD* | *M* | *SD* | |
| Chyatte | 50 | 2034 | 176 | 0.466 | 0.278 | 0.86 |
| Friedl | 63 | 2008 | 152 | 0.595 | 0.306 | 0.14 |
| Dondero *et al.* (LA) | 56 | 1951 | 213 | 0.552 | 0.337 | 0.16 |
| (DA) | " | 1901 | 164 | " | " | 0.18 |

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# AUDIOMETRIC MEASUREMENTS BY ELECTROENCEPHALOGRAPHY

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In 1939, H. Davis *et al.*, and P. A. Davis, described the responses to sound in the human EEG at all levels of sleep. These observations were left unused clinically until Doerfler (1948), Marcus and Gibbs (1949, 1951) used these responses to test hearing. Gidoll (1952), Perl *et al.*, (1953) have added to our information about this EEG method. Grossman (1949) successfully used the local loss of these responses to sound to detect structural cerebral lesions. Passouant *et al.*, (1952) have used sounds to activate the EEG during sleep. Chafetz and Cadilhac (1954) used sounds as a test to study the effects of barbiturates on sleep. Gastaut *et al.*, (1954) have shown local EEG activation by sound in certain epileptics.

In 1953, the pediatricians and otologists in Detroit requested help by EEG in evaluation of hearing in non-communicating pre-school child and infant. Clinically, we have not used the results from EEG alone but have combined them with data from clinical observation, audiologic measurement and behavior patterns in school and home. This combined effort has rarely failed to achieve a useful diagnosis and a realistic therapeutic program. Such combined efforts are hope for the future of hearing studies in infants.

## METHOD

I. *Patients.*

At present 250 patients ranging in age from 3 months to 27 years have been tested by this EEG method. The statistical data in this study is derived from measurements made on 22 patients whose auditory performance was well known. Fifteen of these were from a school for the deaf.

II. *Standard Audiometric method.*

The children were tested with routine audiometric procedures using an ADC 50-E clinical audiometer in a sound absorbent room to determine their thresholds for pure tones. The subjects were tested within 2 to 6 weeks of the EEG test.

The study with pure tone audiometer was followed by tests for speech thresholds (free field thresholds) with a speech audiometer.

We have approached the determination of thresholds with these concepts. With increasing intensity there is an increasing probability of obtaining a response. A threshold may be defined as the intensity level at and above which the patient is more likely to respond than not (the level of 50 per cent response). Such a threshold is therefore bracketed by two intensity levels between which there is a maximal difference in the probability of positive responses. Two extremes are logically possible. In one, the two intensity levels that bracket the threshold are close together in decibels, in the other they are far apart. The former is seen in a patient with nerve deafness. In such a patient the probability of response may rise rapidly from almost complete failure to almost 100 per cent response within an increment as small as 5 decibels. The point of 50 per cent response is easy to determine. The latter or other extreme has been witnessed in aphasic patients or individuals with otosclerosis, etc., in which there might be variations as great as 20 to 80 decibels from the condition of almost no response to the condition of almost total response. In the latter case the point of 50 per cent response is difficult to determine accurately. We must remember also that the

point of 50 per cent response, whether accurate or not, is only one point on a complex function and that one point does not determine the form of that function.

III. *EEG Method.*

Stated simply, this process was to stimulate the sleeping child with pure tones and to observe any resulting brain wave change.

(*a*)*Sedation.* Sleep was accomplished by sedation with secobarbital sodium. We gave ½ to ¾ grains orally at 7 a.m., again at 11 a.m. and finally at 1 p.m. when the test began. If needed the last dose could be doubled or tripled, depending on the patient.

(*b*) *Audiometer.* Sound stimuli were generated by a Maico Audiometer (type H-1) and delivered through earphones.[1] The tones produced had a rise time of 600 msec. and a decay time of 50 msec.

(*c*) *Physical Facilities for EEG.* The dimly lighted testing room was not sound deadened, but was sound shielded from the outside corridor. The ambient noise level varied from 48-58 db. with 53 db. average. The noise level measurement was made with the noise meter set on the 70 db. weighting network. This network made the meter operate with a frequency characteristic equivalent to the human ear at its 70 db. loudness contour. This level is equivalent to those found in most non-residential locations.

(*d*) *EEG Leads and Equipment.* Leads were applied with bentonite paste to zones of the scalp over frontal, central, occipital and temporal areas of the cortex. A lead on the vertex was used as a ground. Both scalp to ear and scalp to scalp recordings were made routinely. Either 6 or 8 channel Grass electroencephalographs were used for recordings. They were operated in the same room with patient and audiometer. The electric motor of the paper drive in the EEG machine produced a steady hum that was clearly audible in the testing room but did not change ambient noise level.

(*e*) *Procedure to Obtain Thresholds.* 1. Non-auditory stimuli of light on eyelids, touching skin of arm or leg, olfactory substances on cotton held under nose and vibration of chair or cot were used to compare with responses to sound since the subject was presumably not deficient in response in all modalities. This also helped to describe the type of EEG change to be expected under the existing experimental state. 2. Clicks were generated by toy crickets and used at fixed distances from the patient before earphones were applied. The cricket gave a pair of clicks at brief intervals. The threshold of response to such a pair of clicks was evaluated for comparative purposes in terms of greatest distance consistent with a positive response. The use of clicks helped establish roughly the intensity level at which to begin study of responses to pure tones. 3. Pure tones generated by the audiometer were presented for periods of 4 to 10 sec. Intensities used were from —10 to 100 db. in 10 db. steps (0 db. average normal human threshold). Frequencies used were in octaves from 125-8000 c/sec. but 500, 1000, 2000 and 4000 were most commonly chosen. Intervals between stimuli were varied from 8 to 90 sec. The method considered best was a tone of 5 sec. duration presented at intervals varied at random anywhere between 35 to 80 sec. Variations of the interval, frequency, intensity and ear used, tended to avoid the possibility of constancy of pattern of stimulation. Random presentation also helped to keep a "surprise" element in the stimulus and prevented conditioning (Passouant 1952, and Chafetz 1954).

We believed the best approach was a relatively subjective one. That is, we tentatively interpreted results as we progressed and varied procedure accordingly. The record was independantly interpreted later for final analysis.

## RESULTS

### I. *Response to pure tones*

A. *Latency of first response.*

There was a relatively long and variable latency before the first EEG change or on effect. The average was 0.7 sec., but variations

[1] We are grateful to Mr. Troy Grady, Maico representative in Detroit who placed a new instrument at our disposal for this work and who was encouraging and constructive in criticisms.

from 0.1 to 3.0 sec. were common (fig. 1 — compare lines 2 and 3). We considered a maximum latency of 3 sec. as still compatible with reliable response. With any longer latency it was difficult to distinguish response from spontaneous fluctuations. Since rise time of their appearance as follows: (1) an *on effect* (0.1 - 3.0 sec. latency), (2) a *continued response* (from on effect till termination of stimulus), (3) an *off effect* (within 2 sec. of cessation of stimulus) and (4) *delayed reaction* (5 - 30 sec. later).

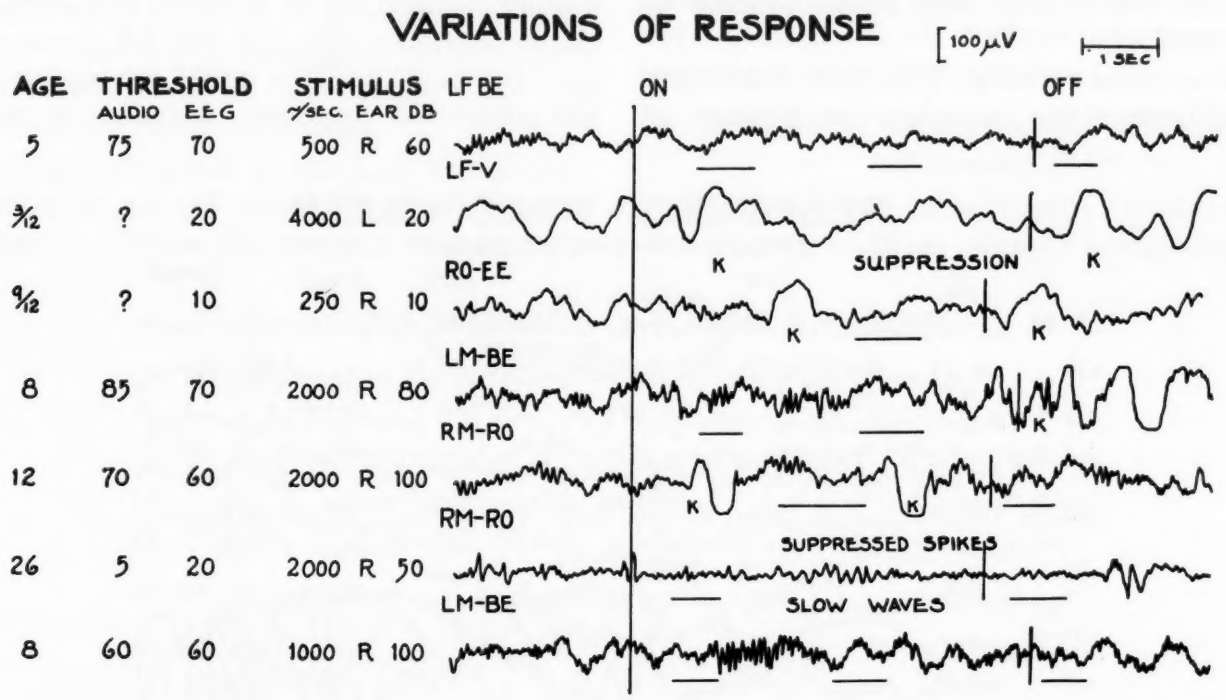


Fig. 1

Seven single strips of EEG records from 6 different patients are alined at the onset of each stimulus. The columns reading from left to right give age in years, audiometric threshold, EEG threshold, and the frequency, ear and intensity of tone presented during the EEG strip. All intensities and thresholds are given in decibels of hearing loss relative to normal level of human threshold. Electrode derivations are L — left, R — right, F — frontal, M — motor, O — occiput, BE — both ear lobes and V — vertex. The remarks on the EEG strips are at the periods when the components of response were detected. Dashes — no response, K — K formation, etc. From top to bottom the strips illustrate reactions to increasing intensity levels relative to audiometric and EEG thresholds.

Line 1 — Failure of response to tone below threshold.
Line 2 — Response at threshold (normal intensity level) in a 3 month old child with 4 deaf members in family.
Line 3 — Response 6 months later in same child as in line 2. Response shows longer latency of on effect.
Line 4 — Only an off effect with a tone below audiometric but above EEG threshold.
Line 5 — Two K patterns during period of stimulation.
Line 6 — Responses from an adult with 2 unusual components.
a. Loss of abnormal slow spikes.
b. A train of slow waves.
Line 7 — Failure to respond to tone of maximal intensity.

time to full intensity of stimulus was 600 msec., we were not able to tell precisely at what time the sense organ responded and therefore did not measure the minimal latency with accuracy.

B. *Timing of the four components of response.*

We have arbitrarily separated the responses into four components based on the

C. *The composition of the four components of response.*

Any one of five varieties of EEG change constituted one of the four components of response.

1. *Decreased activity.* Any one or several of the frequencies present in the EEG pattern in the moments before stimulation was reduced in voltage for a period lasting two

or more seconds (fig. 1, lines 2 and 6, and fig. 2A). This reduction of voltage was usually seen when the intensity was near threshold and was some part of nearly all reliable responses. Reduced voltage occurred as an on effect, continuous response or off effect. It was usually seen as the continuous component.

2. *Increased activity.* The other four kinds of responses were increases in voltage of rhythms already present or new ones that had not occured for the last 30 sec.

(*a*) The K formation described by Davis *et al.*, appeared at threshold or was more certainly seen 10 to 30 db. above (fig. 1, lines, 2, 3 and 4, fig. 2A and B, and fig. 3A and B). This complex most commonly appeared as on and off effects. The K formation was a complex of faster rhythms of 6 to 15 per sec. superimposed on 2 to 5 per sec. waves. There were wide variations of the K complex. Some K formations were composed principally of rhythms faster than 10 per sec.; others of rhythms slower than 10 per sec. The K formation was a most reliable form of response and the most common one.

(*b*) A form of increased activity was a gradual increase in slow and fast waves producing a build up of activity different from the background (fig. 2B and 3A, areas marked "increase"). This build up appeared as the continued response. A build up was reliable if followed by marked voltage reduction or a K formation as the off effect. The build ups occurred more frequently in the lighter levels of sleep.

(*c*) A response could be a spindle of 12 to 13 per sec. waves. These responses occurred in light sleep when spindles of 12 to 14 per sec. waves were present spontaneously or when the pattern was in transition towards this level. A spindle of response was considered reliable only when it appeared clearly out of the rhythm of previous non-evoked

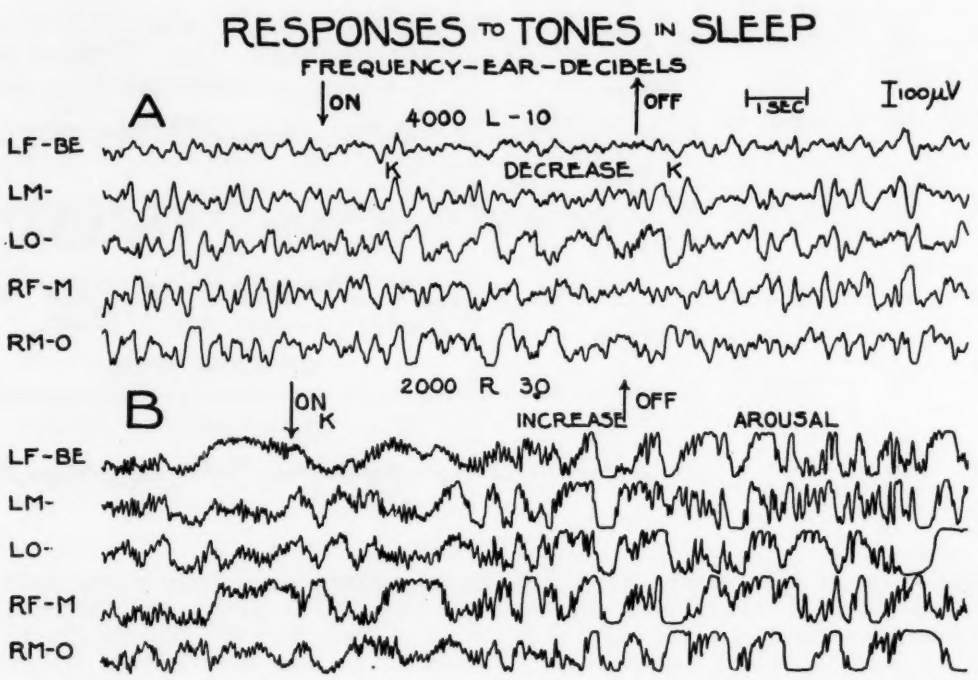


Fig. 2

A. Response from a 4 year old child to 4000 c/sec. to left ear at —10 db. On effect was a K, continuous effect was a decrease of voltage, off effect was a K and there was no delayed reaction.

B. Response from a 9 year old child to 2000 c/sec. to right ear at 30 db. This is also 30 db. above this childs threshold by EEG. There is a K for an on effect and a voltage increase or build up as continuous response. The off effect is lost in the transition of the continuous response into an arousal reaction.

spindles. Spindles occurred as on and off effects. More often the loss of spindles was observed as part of decreased activity.

(*d*) A response could be the appearance of alpha rhythms or the constant 5 to 7 per sec. waves at high voltage of children. These responses were referred to as arousals. These changes were often associated with muscle potentials and visible movement since the child was partially awakened.

Arousals occurred as the continuous component or as an off effect (fig. 2B marked "arousal"). When the patient was in light sleep we noted that sometimes after giving a typical or partial response to the 5 sec. presentation of pure tone and returning to the basic pattern there would be an arousal 5 to 30 sec. later. These responses signaled approaching wakefulness and were classified as delayed reactions. Table I summarizes these responses. There was wide variation from one stimulus to the next as to which components were most clearly present. Figure 1 shows some of the variations in form of the responses with intensity, age and when abnormal EEG rhythms are present.

D. *Location of response.*

As described by previous workers (Davis 1939; Perl 1953, and Gidoll 1952), there was no localization of responses. These responses were present in all regions but were most prominent in central areas.

II. *Analysis of responses and determination of thresholds*

Every record was finally analyzed by viewing a 20 to 30 sec. sample containing each 5 sec. period of stimulation. A decision was made about the presence and character of on effect, continuous response, off effect and delayed response without knowledge of frequency, intensity or ear stimulated. The total response to each tone presentation was given a rating on a scale of 1 to 5. The basis for these ratings were:

No signs of any component: 1

One component present: 2

Two or more components present but con-

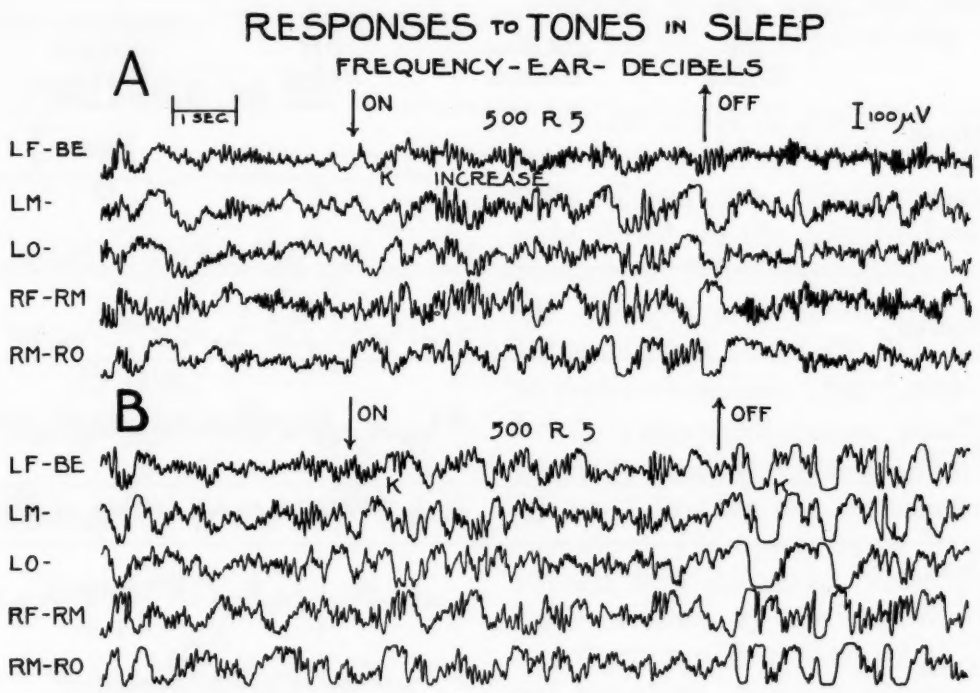


Fig. 3

Illustrations of two different kinds of responses from a 9 year old patient with normal hearing, shows a response to 500 c/sec., left ear at 5 db. This response is a period of constant voltage increase during the period of stimulation. A possible K formation may be separated as an on effect. There is no increase of activity as an off effect. B shows a response to 500 c/sec. in right ear at 5 db. This is made of a K as on effect, no continuous change and a K as off effect.

fidence in response weak: 3
Two or more components present and strong confidence: 4
Two or more components present as well as a definite delayed reaction, usually with muscle potentials: 5

When any two or more of these components were present the response was considered positive (ratings 3, 4 or 5). The presence of one component alone, regardless of how strong, was considered as negative (rating 2). Separate evaluation of these components aided greatly in distinguishing spontaneous changes from true responses. It was unlikely that two spontaneous changes would have occurred at exactly the correct time in relation to stimulus, although one change might easily have appeared. We accepted as threshold the minimal intensity level at and above which stimuli evoked a positive response 50 per cent or more of the whose responses to pure tones required relatively much less intensity.

III. *Responses to clicks*

Click stimuli evoked strong K formations and sometimes voltage reduction. The deaf child required louder clicks to produce these K formations. There was another group of children with disturbances in communication whose precise clinical diagnosis was not clear, who also had raised thresholds to clicks but time (see fig. 5 — compare areas marked 4000 L/20 and 4000 R/20 with 500 R/10).

IV. *Responses to stimuli of other modalities*

The most potent non-auditory stimulus which evoked a K formation was a light tap on chair or cot on which the patient lay (vibration). Vibration often gave responses even when other reactions were absent. Tactile,

TABLE I

RESPONSE COMPONENTS

| EEG CHANGES | | *On Effect* | *Constant Change* | *Off Effect* | *Delayed Change* | *Sleep Level* |
|---|---|---|---|---|---|---|
| *Decrease* | Decrease in Voltage 2 sec. | + | ++ | + | O | Deeper |
| *Increase* | K Formation | ++ | O | ++ | O | Deeper |
| | Build-up of Voltage | O | ++ | O | O | Lighter |
| | Spindles | + | O | + | O | Lighter |
| | Alpha or 5-7/sec. and Muscle | O | + | + | ++ | Lightest |

This table shows what kinds of responses were most likely to occur as on, continuous, off and delayed effects in the different sleep levels.

*Sleep Level*

Deeper: signifies an EEG pattern in sleep containing a strong delta activity.

Lighter: signifies a pattern with spindles, theta waves and central humps, but no or minimal delta.

Lightest: signifies the patterns of low voltage theta waves with few spindles.

visual and olfactory stimuli produced K formation and/or periods of voltage increase or decrease.

### V. *Factors modifying these EEG responses to sound*

There was constant variation in the composition and even the presence of these responses to stimulation above threshold. Below is a discussion of the possible role played by each factor which presumably could cause these variations.

A. *Age.* Over the range of 3 months to 27 years of age there were no essential differences in these responses. The same forms

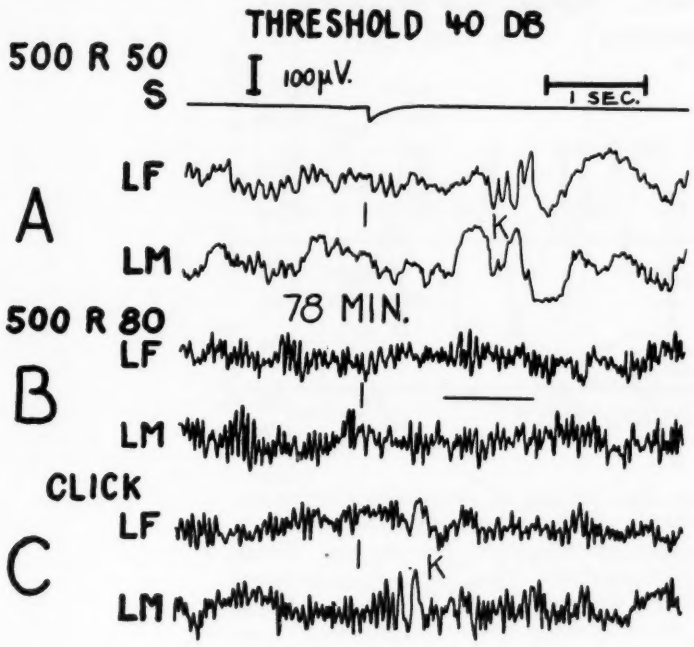


Fig. 4

A type of change in EEG pattern seen during auditory study which is accompanied by elevated thresholds or loss of responses. Loud noises (clicks) and speech may still be effective. S — signal for onset of stimulus. All electrode derivations are from scalp lead indicated to both ears. Sample A was taken early in the study. Response to tone 10 db. above threshold. Sample B and C were taken 78 min. later. B shows failure to respond to tone 40 db. above threshold. C shows response to click still present but abbreviated. No Secobarbital given since prior to start of test.

of response were present and they were as accurate in determining the threshold of the infant as of the adult.

B. *Brain damage.* Children whose problems included brain damage as either a proven or probable part of their diagnosis gave less consistency of EEG responses and therefore had less clear thresholds. As described under standard audiometric method, the intensities bracketing the threshold in these cases were far apart. Consequently, the minimal intensity giving 50 per cent response was not a sharp point. Such a threshold was difficult to determine accurately. The presence, however, of slow spikes or other focal EEG disturbances did not in itself interfere with accurate EEG thresholds. Occasionally the slow spikes or abnormal EEG discharges changed in response to the stimulus (fig. 1, line 6). A full EEG seizure discharge 40 sec. long was evoked once by a brief period of rhythmically repeated bell tones.

C. *Intensity of stimulus.* There was little apparent relationship between decibels and form of response. With increase in intensity near threshold the amplitude and complexity increased. When over 30 db. above threshold the changes were more gradual and subtle. Intense tones (over 70 db.) sometimes failed to evoke a response (fig. 1, line 7).

D. *Interval between stimuli.* There was no evidence of a refractoriness between 3 and 80 sec. following the termination of the first stimulus. If, however, a long sequence of stimuli was delivered, then the interval became critical. If the stimuli were presented at intervals of less than 30 or 40 sec. or without variation, then the subject either aroused rapidly or there was a failure of responses to appear at a detectable level (fig. 5, areas marked 4000 L 20 and 4000 R 20).

E. *Depth of sleep and action of secobarbital.* In the lighter stages of sleep, as estimated by EEG pattern, there were more responses made of spindles, decreased voltage, arousals and delayed reactions. In deeper stages, K formations, reduced voltage and off effects were more usual (table I).

The depth of sleep fluctuated rapidly and the pattern of EEG response was as variable as the level of sleep. Since the stimuli tended to arouse the sleeper, there was always an equilibrium maintained between staying asleep and waking up. This equilibrium was upset whenever any marked change occurred in the pattern of presenting stimuli. The sub-

ject tended either to wake up or to become less responsive.

We recognized two general trends in the EEG pattern in sleep induced with sedative. One was composed principally of slow waves, 1 to 6 per sec. with or without spindles and central humps. When this pattern was present there were good responses and clear cut thresholds. The other trend was seen in the EEG as composed mostly of fast waves. There were two kinds of fast patterns that were relatively unresponsive. One was composed of fast activity of 18 to 25 per sec. waves in frontal areas due to barbiturate action as unresponsive patterns were present the K formations were shorter in duration, more difficult to distinguish from the background and continuous responses were lost (fig. 4). In this state threshold measurements were unreliable.

F. *Extinction.* If the results of any one study were plotted so that the rating of responses (1 to 5) were expressed as a function of time (fig. 5), it was seen that periodically there were no detectable responses to stimuli at or well above the eventually determined threshold (Chafetz and Cadilhac 1954). The responses to stimuli well above threshold,

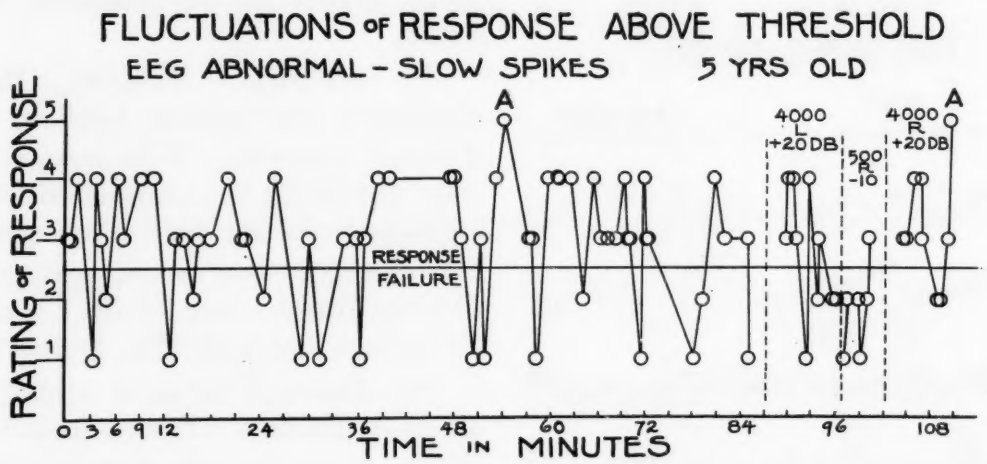


Fig. 5

This illustrates the relationship between the rating of responses to tones above threshold and the time of presentation during the course of one test. At the left some of the more rapid cycles of response are shown. From the 35th to 54th min. is seen the characteristic rise in responsiveness followed by a quick extinction just before arousal (A). In many of the intervals between these responses there were stimuli below threshold. These are not recorded. On the right are 3 special periods. In each period a particular pattern of stimulation (frequency, ear and intensity) was repeated. At 4000 L (left ear) at + 20 db. there is a progressive failure of response as the stimulus is repeated. At 500 R —10 db. the stimulus is 10 db. below EEG threshold and only one of 6 presentations was successful. At 4000 on right at + 20 db. a repeated stimulus 20 db. above threshold produces the characteristic pattern which ended in arousal (A).

described by Brazier and Finesinger (1945). These were related in time to recent ingestion or increased doses of secobarbital. The other kind of unresponsive fast pattern was composed principally of 14 to 18 per sec. waves in all areas, slower waves were infrequent and spindles were either difficult to distinguish from the background or were nearly continuous. This pattern was first described by D. Davidson (1955) as appearing in children with a paroxysmally occurring sleep from which they could not be aroused. When these therefore, tended to oscillate from presence to total absence. This waxing and waning was often on a different cycle for different areas of the brain. When the majority of areas viewed failed at one time, this was considered as no response. These cycles usually covered 50 sec. to 3 min. Tentatively we have referred to the time of failures as periods of extinction (for a discussion of extinction described by Dusser de Barène, see Fulton 1943). We presumed it was a failure in the cortex to respond rather than a failure of impulses to

reach the cortex. This cycling could be distinguished from fatigue by the fact that the first stimulus presented might be subject to extinction with good responses appearing later to the same stimulus. Fatigue in this system was not clearly detected.

## COMPARISON OF RESULTS BY EEG AND STANDARD AUDIOMETRY

The comparison is the lead to understanding the relative merits and inherent problems of both methods in obtaining clinically valuable results. At this time we present the results of only the first 22 cases (5 normals and 17 children who were in special class rooms for the deaf). They ranged from 4 to 13 years of age. Peripheral deafness was not the only diagnostic category in the group. This group showed that in any one person the average difference between the two methods varied from 3 to 40 db. The average difference between the two methods for the entire group was 18 db. with a standard deviation of 14.7 db. This wide scatter of data is probably the result of the mixed age and diagnostic categories chosen and the fact that these were run during the earlier period when the EEG technique was developing. Since then experience with 250 cases indicates that a closer or more practical similarity of thresholds can be achieved. We have not applied a statistical analysis to these later cases nor have we separated out the different diagnostic groups at this time. Such an approach may well change our results.

The audiologist was particularly interested in knowing the rules governing the displacement in any direction of the EEG thresholds relative to the standard audiometric thresholds. This information would then make the EEG thresholds useful as a basis for an educational approach with the infant.

The following cases (4 are from the 22 cases referred to above) are presented to illustrate the types of correlation seen (fig. 6).

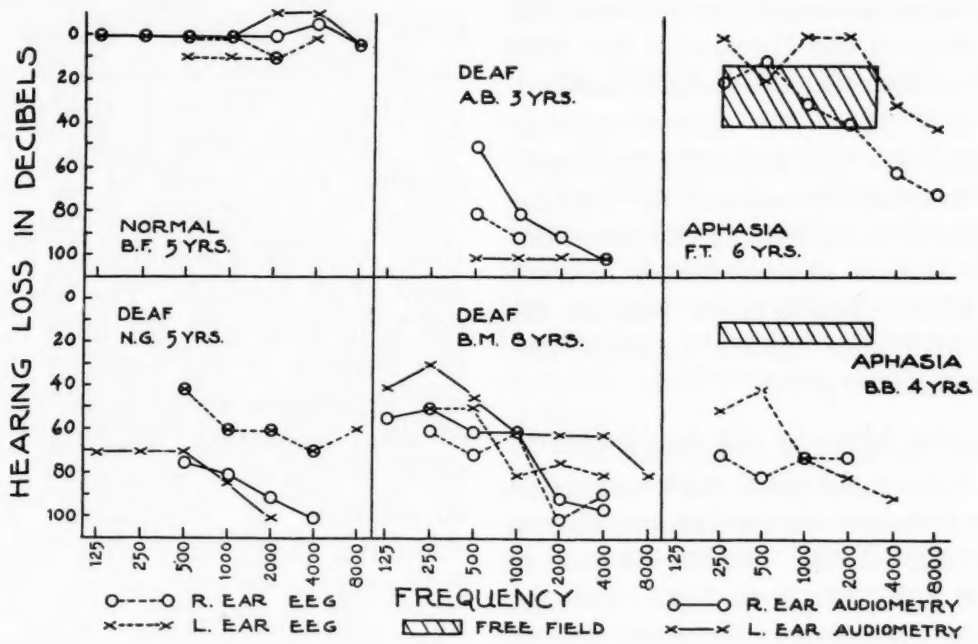


Fig. 6

## COMPARISON OF PROFILES

A. *Close Correlation of Profiles.*

1. Normal hearing case — same thresholds. B. F., a 5 year old normal hearing child was tested by Standard Audiometric Method (S.A.M.) and EEG with the resulting good agreement.

2. Severely hard of hearing, A. B., 3 year old severely handicapped child tested by S.A.M. and EEG with results shown in figure 2. Both methods showed the left ear to be see severely damaged as to be possibly beyond practical use. This child also had an abnormal EEG pattern with slow spikes (seizure discharges) in posterior regions, greater on the left.

3. Diagnostically aphasic child — F. T., an 8 year old child was diagnosed as aphasic by both medical and speech specialists. In figure 3, the range of responses to audiometric tones and speech is shown by the shaded area. Superimposed are the points achieved by the EEG method. Both methods demonstrated either normal hearing or hearing too good to account for the confusion in speech.

B. *Same Profiles — Different Thresholds.*

4. N. G., a 5 year old child receiving special education for the acoustically handicapped. By both S.A.M. and EEG methods the profile of the hearing thresholds was essentially the same although in this case the EEG method showed the thresholds for both ears to be better than did the S.A.M. method.

5. B. M., a 7 year old child receiving special education for the acoustically handicapped. The hearing thresholds or profiles by both methods were essentially the same, but in this case the S.A.M. showed better hearing than did the EEG. Again there was an abnormal EEG with slow spikes (seizure discharges) in posterior regions.

C. *No relationship between the two methods.*

6. B. B., a 4 year old child with a suspected hearing loss because of retarded speech was tested and produced the results shown in figure 4. It is interesting to note that the EEG profile was recorded 12 hours before the child "broke out" with chicken pox. There could have been a peripheral impairment which was not present when observed by S.A.M. In retest of the child (results not shown on graph) the EEG threshold rose approximately to the level of the S.A.M. threshold.

## DISCUSSION

The communication system involves detection of sound by a peripheral sensory mechanism which activates several neural pathways to many cerebral centers. This activity results in reflexes and in alertness, reception and perception of the pattern of stimulation. This response is expanded and abstracted into symbolic thinking and leads in turn to the formation of expressive patterns in gesturing, speaking or writing on the motor side.

Standard audiometry evaluates the sensory process through its ability to evoke a consciously determined motor response. With electrodermal response (Hardy 1951, and Goldstein 1954) a conditioned visceral reaction is used as the indicator of sensory reception Both methods span the entire mechanism, one through the psyche and the other through unconscious adaptive behavior.

In contrast the EEG method measures only the sensory paths which diffusely modify the activity of the central nervous system in sleep. This activity may be totally unconscious and does not involve a motor pathway.

We would expect differences between these three methods. Rather than consider these differences as errors, we prefer to interpret them as revealing functional features of the different arcs tested. The immediate problem then would be to establish the accuracy based upon correlation of results in those patients in whom there is essential agreement of all methods. The latter has, however, not been done with the data in this presentation because it was believed that only extensive experience would allow the correct choice of what constitutes essential agreement. We have, at this time, presented only the general correlation of thresholds determined by standard audiometry with those by EEG. A full analysis of the accuracy of EEG threshold needs more extensive work.

From our present experience we would like to hypothecate that the neural mechanism evoking our EEG response may separate from the primary sensory projection path in the lower centers and activate a non-specific subcortical arousal center. This center in turn evokes the diffuse cortical changes recorded in the EEG.

Both the ascending reticular activating system in the midbrain (Moruzzi and Magoun 1949) as suggested by Appaix (1954), or the cingular gyrus in the temporal lobe (Ward 1948) are possibilities for such a center. Our evidence to substantiate this hypothesis is expressed in the contrasts between the EEG reactions and the functioning of the path for discriminative hearing.

1. The EEG response is not influenced by

the age of patient, indicating it is a primitive path and matures early.

2. The response shows no localization on the cortical surface while the primary projection path is sharply localized anatomically.

3. The response has a long and variable latency, indicating a complex path.

4. The response is exactly like that produced by other modalities, i.e., vibration, touch, etc.

5. The responsiveness of this path shows greater variation than would be expected in the route of a constantly used sensory modality.

Knowledge of the laws governing the activation of such a center will play an important part in making useful the EEG responses.

We would like to offer a tentative explanation of the failure of response to pure tone when the fast EEG pattern of Davidson is present (fig. 5). Pure tone with a slow crescendo onset may depend upon temporal summation to reach the threshold of activation of the arousal mechanism. In sedated or certain light sleep states, temporal summation may be decreased and therefore stimuli rising slowly to maximum would lose effectiveness. Rapidly rising stimuli with a strong component of spatial summation should still be effective. This concept is consistent with the observation that clicks, speech, bells, etc., will still produce some response in the same "fast" sleep pattern. We presume these latter stimuli work by spatial summation since they activate a wider area of the basilar membrane in the cochlea and consequently more nerve fibers in a brief time span. There is apparently independent variation of response to click and to pure tone implying some difference in underlying mechanism activated (see under Results, III. Responses to clicks, p. 472).

The EEG responses we have described offer the physiologist another way of measuring the changing states in the cerebral network. To the clinician they offer another method of evaluating hearing accurate to at least plus or minus 18 db. and may be of particular use in testing infants. To the audiologist this method offers help in some of the controversial patients and the opportunity through contrast to learn more about all methods of testing.

To all three it offers other ways of expanding our knowledge of the auditory mechanism.

## SUMMARY

The EEG pattern in children in secobarbital sleep showed responses to the presentation of tones generated by an audiometer. These responses consisted of an on effect (usually a K formation), a continuous effect, and off effect and a delayed reaction (arousal).

Any intensity of tone was considered to be above threshold when it evoked a positive EEG response 50 per cent or more of the time.

The thresholds so determined in 22 selected cases agreed with those obtained by standard audiometry to within plus or minus 18 db.

Variations in response occurred with depth of sleep, quantity and type of sedative, pattern of stimulation presented, changes in the experimental procedure in the midst of the testing, as well as unknown factors presumably involving the child and mechanisms of sleep.

The discussion suggested that these EEG responses were associated with some simple arousing system in the central nervous system because they were diffuse, not influenced by age from 3 months to 27 years and capable of being duplicated by other sensory modalities.

These thresholds have great clinical usefulness if combined with all other information and not made the sole basis for clinical judgement. They extend the measurement of auditory profiles into those infants and handicapped children who do not communicate.

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# THE ELECTROENCEPHALOGRAM IN DEMENTIA. — SOME PRELIMINARY OBSERVATIONS AND CORRELATIONS

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## I. INTRODUCTION

In assessing mental changes associated with organic brain disease we have used, among other techniques, the EEG, in an effort to determine if there are associated abnormalities in the brain waves and if these abnormalities are quantitatively related to the degree of mental disturbance. This paper reports a series of such patients studied on a psychiatric service. Certain findings will be presented to indicate that not only do the majority of these patients have EEG abnormalities, but there appears to be a correlation between degree of mental change and degree of brain wave change which suggests that the EEG may be used as a diagnostic and prognostic tool in the appraisal of patients with organic brain disease. We also attempt to clarify the mental findings in these disorders and elaborate our concept of dementia.

The EEG has come to be a useful diagnostic instrument in various medical conditions in which disturbances of cerebral metabolism are manifest, ever since Romano and Engel's (1944) original work on delirium. The physiological basis of the relationship between cerebral metabolism and brain waves had been earlier demonstrated by Lindsley and Rubinstein (1937), Hoagland (1936, 1938), and the Davises (1938). The latter workers showed that in general there is a reciprocal relationship between cerebral metabolic rate and brain wave frequency, and between blood oxygen tension and blood sugar level and alpha rate.

One of Romano and Engel's (1944) important contributions was the elucidation of the state of "delirium", marked by a reduced level of awareness (consciousness), related physiologically to an impairment of cerebral metabolism, and revealed by a slowing of the EEG frequency generally proportional to the degree of metabolic impairment. Delirium may range from subtle disturbances of consciousness often undetected by the clinician to severe states of stupor and coma, and is a reversible state depending on correction of the underlying cerebral metabolic disturbance. Thus the EEG is of significant assistance to diagnosis and prognosis of these medical disorders associated with delirium.

We have been interested in the similar application of the EEG to problems of organic brain disease which are marked not only by impaired cerebral metabolism but presumably also by certain damage to or alteration of cerebral tissue. These conditions include the various inflammatory, toxic, degenerative, vascular, neoplastic, and traumatic afflictions of the brain, which present, aside from various neurological signs and symptoms and various mental disorders, a rather common psychological state which has gone under many names (organic psychosis, organic syndrome, chronic brain syndrome, mental deterioration, etc.). We prefer to call this syndrome dementia and feel it is a common denominator in organic brain disease. It may be regarded as a more or less irreversible and generally progressive impairment of intellectual functions accompanying structural brain changes. These functions include the modalities of the sensorium such as attention, memory, orientation, retention, recall, calculation, and ab-

stract thinking. Usually, a pattern of disorganization obtains, in which "higher" and more complex functions such as abstract thinking are impaired first, to be followed by memory disturbances, disorientation and finally complete dissolution of sensorial capacities in the severe states of dementia. This syndrome also comprises various emotional and behavioral changes which can be thought of as "release phenomena" consequent to impaired ego control and loss of function. One of us has considered this elsewhere from a dynamic psychological viewpoint (Schuster 1952). In general, these changes are in the direction of increased emotional lability, loss of emotional control, and emergence of various infantile and "regressive" patterns of behavior.

It is well to point out that delirium and dementia should not be thought of as completely separate entities, but rather one should consider that delirium may, if it produces certain irreversible damage, become a dementia. On clinical grounds alone, it is sometimes impossible to differentiate between the two; therefore, one often must introduce inferential data — age of the patient, presence or absence of hypertension and vascular disease, history of drug intake, presence of specific infectious or inflammatory agents, etc. Also, it is wise to bear in mind that delirium and dementia are essentially clinical terms; and while metabolic disturbances have been well correlated with delirium, as yet no such definitive correlation between brain tissue damage and dementia exists. For the time being one can view these two clinical syndromes as two points in a continuum which share certain common features (e.g. reduced level of awareness) but are differentiated largely by the degree of their reversibility.

One way of studying the problem of dementia is by anatomical means. So far, however, the question of correlation between degree of dementia demonstrated clinically and amount of underlying brain damage elicited at autopsy remains unanswered. At best one must conclude that there is no direct relation, as indicated by the work of Malamud (1950) and Rothschild (1942). That is, some patients with severe impairment of intellectual functions may show slight evidence of neuronal damage; and, conversely, a patient showing no clinical evidence of dementia may at autopsy by found to have profound brain damage.

Physiological techniques available for studying organic brain disease and dementia are those of cerebral metabolism, blood flow, and the EEG. Freyhan *et al.* (1951) have demonstrated reduced blood flow and cerebral metabolic rate in psychoses of senility, and Williams and Gibbs (1939) found that in active cortical degeneration slow brain wave potentials are produced.

There have been a number of published reports on EEG findings in various conditions manifesting organic brain disease and dementia. Most of these have approached the topic from the standpoint of brain wave abnormalities found in specific conditions. The consensus in these studies is that the majority of patients thus afflicted will have EEG abnormalities regardless of whether the underlying pathology is associated with senile dementia (Mundy-Castle *et al.* 1954), cerebral arteriosclerosis (Liberson *et al.* 1945, and Hill 1950), paretic neurosyphilis (Callaway 1945, Finley *et al.* 1942, Greenblatt *et al.* 1944, Merritt *et al.* 1946, and Seeley *et al.* 1953), Korsakow's psychosis (Gorman 1950 and Greenblatt 1944), Wilson's disease (Weatherley 1941), Huntington's chorea (Patterson *et al.* 1948), arsenical encephalopathy (Roseman 1950), or Japanese B encephalitis (Aring 1949). The EEG abnormalities found most frequently are the presence of slow waves and increasing voltage, although a preponderance of low voltage, fast rhythms has been reported in the arteriosclerotic group (Yeager *et al.* 1937).

The progression and activity of brain changes seem to be a factor in the production of EEG abnormalities. Cohn *et al.* (1949) found no EEG abnormalities in patients with arterial hypertension when no clinical evidence of gross brain lesions obtained, but with rapid progression of clinical symptoms, serial tracings taken over periods of one to three years showed increasing voltage and slow wave activity.

In the studies cited there is little agreement as to correlation of the degree of EEG abnormalities and the severity or duration of the disorder, although Finley (1942) in his study of paretic neurosyphilis states that the more severe the dementia the slower the rhythm is likely to be. Not until Mundy-Castle and co-workers' recent work (1954) has an attempt been made to correlate the degree of clinically observable dementia with EEG abnormalities. In a study of 119 cases of senile psychosis, cerebral arteriosclerosis and presenile dementia they found an incidence of 54 per cent slow wave abnormality, the most characteristic findings being diffuse delta and theta rhythms which occur most often in the most severely demented patients. They also found a statistically significant decrease in alpha-index corresponding to an increasing degree of dementia. There was no relationship between slowing of the EEG and different disturbances in mood or thought content in these patients.

We feel that confusion has resulted from these studies because of their *ad hoc* approach to specific disorders; their failure to view dementia in generic terms, as a clinical syndrome common to many different disorders involving organic brain disease; in their failure to correlate degrees of dementia and EEG changes; and in their failure to differentiate dementia from psychotic manifestations which may occur with or without dementia. We present our data with the intention and hope of clarifying these issues.

## METHOD AND MATERIALS

Our material consists of 71 patients (see table I) from the psychiatric and medical division as well as the private offices of the Strong Memorial and Rochester Municipal Hospitals. The patients were chosen because of the presence of dementia associated with a variety of clinical conditions known to produce diffuse, non-focal brain changes. Patients with brain tumor, cerebral thrombosis and other localized processes, as well as idiopathic convulsive disorders were not included. No regard was paid to age or sex in selecting the material (32 were men and 39 women). Many of these patients had a history of months if not years of progressive behavioral change and intellectual impairment: the longest history being years and the shortest approximately two weeks (CO poisoning). The temporal details relating to onset may be inaccurate in these conditions, because the dementia, especially if slow in onset, may go undetected by the patient and family for some time.

TABLE I

NUMBER OF PATIENTS ACCORDING TO CLINICAL DIAGNOSIS

| | *Male* | *Female* | *Total* |
|---|---|---|---|
| Early cerebral arteriosclerosis | 5 | 9 | 14 |
| Late cerebral arteriosclerosis | 14 | 19 | 33 |
| Senile dementia | 3 | 6 | 9 |
| General paresis | | 1 | 1 |
| Presenile dementia | 4 | 2 | 6 |
| Korsakow's psychosis | 3 | | 3 |
| Alcoholic deterioration | 1 | | 1 |
| Dementia due to CO. | 1 | | 1 |
| Dementia cause unknown | 1 | 2 | 3 |
| | 32 | 39 | 71 |

Forty-seven of the patients suffered from cerebral arteriosclerosis, 14 of whom were in the early stages of this condition. This diagnostic label was attached on the basis of a history of fluctuating dementia with variability of performance from one time to another, attacks of nocturnal confusion, vertigo, headache, presence of systemic hypertension, evidence of arteriosclerosis, and X-ray evidence of calcification of intracranial blood vessels, especially of the internal carotid arteries.

The diagnosis of senile dementia (9 cases) rested on the patients' dementia developing in the senium (advanced age), a gradual onset unmarked by a fluctuating course and an absence of prominent indications of hypertension and arteriosclerosis.

The diagnosis of presenile dementia was made on the tentative basis of a non-specific dementia occurring in the pre-senium (all patients were under 57 years of age). They all had a history of at least three years duration. In none was there a pneumo-encephalogram or cortical biopsy done to confirm the clinical diagnosis.

Three patients who had Korsakow's psychosis all had been heavy drinkers for many years, demonstrated amnesia for recent events, disorientation, confabulation and peripheral neuropathy.

In addition there was one patient with general paresis who had a history of untreated syphilis and presented clinical, spinal fluid and blood serology evidence of this disorder; another with long standing alcoholism and dementia not typical of Korsakow's psychosis and whom we labeled "alcoholic deterioration"; and one patient who had made a suicidal attempt with illuminating gas, was exposed to it for several hours and thereafter was demented. Finally, there were three patients aged 35, 47, and 66 years who were demented but in whom no etiology could be established.

None of our diagnoses were corroborated anatomically or pathologically, as no deaths occurred in our series at the time our data were organized.

All patients who on complete neurological examination revealed evidence of focal signs were excluded from study. Care was taken not to include patients who were delirious. Thus patients with a history of drug intake or who were found to be suffering from congestive heart failure, chronic pulmonary disease, diabetes mellitus, secondary anemia, pernicious anemia, adrenocortical insufficiency, nitrogen retention, thyroid disease, etc., were excluded from this study. Suspected increased intracranial pressure of whatever cause was ruled out, insofar as this is possible, by physical examination, skull X-rays, and lumbar puncture (28 cases).

Each patient had a complete medical, neurological and psychiatric evaluation, and all patients were seen by one or other of us. Besides observing the patients' overall behavior, mood, stream of talk and thought content, the sensorium was examined. We tested a variety of functions or modalities of the sensorium, including: attention (by means of serial subtraction of 3's or 7's from 100), calculations, retention and recall, abstract thinking (proverbs and abstraction tests), recent and remote memory, orientation, and general information. There was a uniform examination of all these functions done on all patients, repeated whenever any clinical change or variability was noted. Every patient had at least three such examinations over a minimal period of ten days. Some of the patients studied, however, were followed for several months. Particular attention was paid not only to accuracy but also rate of performance. Whenever the diagnosis of dementia was questionable, more refined psychological tests were performed to rebut or substantiate the diagnosis — the Wechsler-Bellevue, Goldstein-Scheerer and Rorschach tests being most frequently employed (in 16 cases).

In this study we felt it important not only to ascertain carefully the presence of dementia but also to make some attempt to grade the degree of dementia present, and if possible to correlate the varying degrees of severity of dementia with varieties of EEG abnormalities. With this in mind and from previous clinical experience we evolved the following rough classification of dementia.

Grade I. *Minimal dementia,* in which only minor disturbances such as attention span and some impairment of abstract thinking are observed.

Grade II. *Moderate dementia,* in which in addition to minor disturbances (above) there are also defects of recent memory, retention and recall and difficulty with calculations and serial numbers.

Grade III. *Severe dementia,* in addition to the disturbances noted above, there is impairment of remote memory, orientation, and any additional signs of gross disorganization of the thinking processes.

Each patient had at least two electroencephalograms taken. These were recorded by the same technician using a Grass 6 channel and later 8 channel recording machine. All the tracings were read by one of us. If on sensorial testing any marked changes in performance were noted from previous examinations, the electroencephalogram was repeated. We also set up a simple classification of EEG abnormalities:

*Type I.* Normal EEGs, consisting of records with a basic frequency of 8-12 c/sec. or low voltage fast tracings.

*Type II.* EEGs with predominant beta rhythm, namely 13 c/sec. of significant voltage ($< 30\ \mu$V.).

*Type III.* EEGs containing rhythms predominantly in the theta range, i.e. 4-8 c/sec.

*Type IV.* EEGs containing rhythms as slow as the delta range, i.e. 1-3 c/sec. These records contained also much theta rhythm.

Types I, III and IV represent an increasing degree of slowing, aside from 3 fast records (type II). There were no mixed fast and slow types, nor any "seizure type" of record in our series, as described below.

## RESULTS

Of our 71 patients with dementia (table II) only 16 (22 per cent) had normal EEGs; 55 patients (78 per cent) had abnormal tracings (i.e., types II, III, IV). Secondly, the predominant abnormality was a non-focal slowing, either diffuse or scattered, but never of a seizure-burst type of discharge (i.e. high voltage slow and spiking discharges). Only 3 records were predominantly fast (type II). This is unusual considering the observation of high incidence of fast rhythms in the older age group. Thirdly, one can see from table III that there is a certain direct relation between degree of dementia and degree of EEG slowing. For example, almost half (8 out of 19) of those with minimal dementia (grade I) had normal EEGs, and none had the most severe degree of slowing (EEG type IV). On the other hand of 30 patients with severe dementia (grade III), only 2 had normal tracings and 27 had either type III or IV EEG changes. In the group with an intermediate degree of dementia (grade II) 6 out of 22 had normal EEGs, 13 had type III EEG abnormality, and only two had type IV EEG as compared with 8 out of 30 cases of severe dementia who had type IV EEGs.

The data recorded on table III was subjected to statistical analysis as recorded in the footnote to this table. This showed (by the small number chi-square technique) a better than chance correlation between degree of dementia and degree of EEG change for the entire group of patients; but this correlation was statistically significant only in the non-psychotic group of patients. Those with dementia and psychotic trends did not show a statistically significant correlation between degree of dementia and degree of EEG slowing. However, this analysis may or may not be significant, in that it was necessary to "lump together" two grades of dementia (II and III) and two types of EEG (III and IV) which were then compared. Likewise grade I dementia was compared with combined types I and II EEG. In the opinion of the authors more material is needed in future studies in order to obtain a more meaningful statistical appraisal and either confirm or negate our impression that there is a correlation between degree of dementia and EEG change.

TABLE II

INCIDENCE OF ABNORMAL EEG ACCORDING TO DIAGNOSIS

| | *Normal* | *Abnormal* | *Total* |
|---|---|---|---|
| Early cerebral arteriosclerosis (non-psychotic) | 3 | | |
| (psychotic) | 5 | 6 | 14 |
| Late cerebral arteriosclerosis (non-psychotic) | | 6 | |
| (psychotic) | 5 | 22 | 33 |
| Senile dementia (non-psychotic) | | 3 | |
| (psychotic) | 1 | 5 | 9 |
| General paresis (non-psychotic) | | | |
| (psychotic) | | 1 | 1 |
| Presenile dementia (non-psychotic) | | 4 | |
| (psychotic) | | 2 | 6 |
| Korsakow's psychosis (non-psychotic) | | 1 | |
| (psychotic) | | 2 | 3 |
| Alcoholic deterioration (non-psychotic) | | | |
| (psychotic) | 1 | | 1 |
| Dementia due to carbon monoxide (non-psychotic) | | 1 | |
| (psychotic) | | | 1 |
| Dementia unknown cause (non-psychotic) | | 2 | |
| (psychotic) | 1 | | 3 |
| | 16 | 55 | |

| | | |
|---|---|---|
| Normal EEG | 16 | 22% |
| Abnormal EEG | 55 | 78% |
| Total | 71 | |

TABLE III

RELATION OF THE DEGREE OF DEMENTIA TO DEGREE OF EEG ABNORMALITY

NON-PSYCHOTIC PATIENTS (21)

| Degree of Dementia Grade | EEG Abnormality Type | | | |
|---|---|---|---|---|
| | I | II | III | IV |
| I | | | | |
| II | 3 | | | |
| III | 1 | | 5 | |
| | | | 8 | 4 |
| | — | — | — | — |
| % Abnormal EEG 81% | 4 | 0 | 13 | 4 |

PSYCHOTIC PATIENTS (50)

| Degree of Dementia Grade | EEG Abnormality Type | | | |
|---|---|---|---|---|
| | I | II | III | IV |
| I | | | | |
| II | 5 | 1 | 10 | |
| III | 5 | 1 | 8 | 2 |
| | 2 | 1 | 11 | 4 |
| | — | — | — | — |
| % Abnormal EEG 76% | 12 | 3 | 29 | 6 |

TOTAL PATIENTS (71)

| Degree of Dementia Grade | EEG Abnormality Type | | | | |
|---|---|---|---|---|---|
| | I | II | III | IV | Total |
| I | 8 | 1 | 10 | | 19 |
| II | 6 | 1 | 13 | 2 | 22 |
| III | 2 | 1 | 19 | 8 | 30 |
| | — | — | — | — | |
| | 16 | 3 | 29 | 10 | |

1. In order to make chi-square techniques applicable, each table was turned into a 2 x 2 by combining the EEG types I and II together and, similarly, for EEG types III and IV. Dementia grades II and III were also combined.

2. The non-psychotic patients (21) group was significant at the 1 per cent level. If allocation to dementia classes from EEG types are made as given above, the per cent of correct classification is 95 per cent. This is about 23 per cent better than chance allocation.

3. The psychotic patients (50) group shows no evidence of differing significantly from chance. The chi-square is completely insignificant (50).

4. The total patients (71) group was significantly different from chance at the 1 per cent level. If type I and II EEG abnormalities are predicted to be in dementia grades I, and EEG III and IV are similarly allocated to dementia type II and III, the per cent of correct classification is 72 per cent. This is 11 per cent better than chance allocation.

## DISCUSSION

In relating EEG changes to dementia one must consider first of all what changes in the brain occur in the "normal" aging population — older people without dementia. There have been a number of studies in this area which have yielded somewhat conflicting results. Some authors report an increase in the number of slow wave EEGs after the age of 60 (Gibbs *et al.* 1950) or after the age 70 (Davis 1941, O'Leary *et al.* 1951, and Obrist 1951). On the other hand Liberson and Strauss (1941) stated there is a decrease with age of delta activity; although the amount of such activity after hyperventilation is higher than in younger subjects, and those with organic brain disease tend to show a marked increase in slow rhythms after hyperventilation. Mundy-Castle (1951) reports that theta activity is more common in young males than in a 75 year-old group. Many workers do not believe that age alone is responsible for the irregularity and slowing of the EEG and implicate cerebral arteriosclerosis and senile changes (Davis *et al.* 1939). This view has had more recent confirmation by other workers (Greenblatt *et al.* 1945a, and Luce *et al.* 1951). Those aged patients who showed slow rhythms manifested "mental deterioration", whereas those with normal EEGs did not show such mental changes (McAdam *et al.* 1952). Other studies (Barnes *et al.* 1953, Obrist 1954, and Silverman *et al.* 1953) of aged groups both hospitalized and non-hospitalized and free of evidence of brain disease on neurological examination indicate an incidence of slow rhythms varying from 13-56 per cent. Our main criticism of the work cited is that, with the exception of Mundy-Castle's recent study (1954) there has not been a careful appraisal of mental status and estimation of dementia in these groups of aged patients.

It would seem a reasonable conclusion that advanced age alone is not responsible for a high incidence of abnormal EEG findings. The latter seems to indicate the presence of organic brain disease and dementia. Twenty of our patients were 60 or under, and of these 15 had abnormal EEGs.

Our data indicate that not only does the majority of patients with dementia have non-

focal, diffuse slowing of the EEG (78 per cent) but the greater the degree of dementia the more pronounced the EEG slowing. There is a rough correlation between the three grades of dementia we have outlined and the incidence and type of brain wave slowing (see table III and footnote).

Another issue is whether or not etiology of the organic brain disease has to do with incidence or type of EEG changes. Hoch (1941) felt that inflammatory and vascular lesions tend to produce the most profound EEG change. Hill (1948) noted slower rhythms in general paresis and vascular encephalopathies than in chronic diffuse processes of slower onset. This is an unsettled question, but we tend to feel that etiology is not as important as the rate and extent of progress of the brain disease. According to some authors (Hill 1948, and Parsonage 1950) the greater the amount of cerebral tissue involved the higher the incidence of slow rhythms. This conclusion is not entirely borne out, however, by pneumo-encephalographic studies (Courjon *et al.* 1950; Delay *et al.* 1944 a and b; Rubin 1939; Semrad *et al.* 1943; Trowbridge *et al.* 1942) which attempt to correlate degrees of cerebral atrophy with EEG changes. The data are conflicting, although most of the studies demonstrate a high incidence of slow EEGs in those cases demonstrating significant cerebral atrophy.

The rate of progression and acuteness of onset are also probably more significant factors than the etiology. Those cases with an insidious, slowly progressing or arrested course may manifest only slow alpha rhythm (Parsonage 1950) or may be associated with no EEG changes (Greenblatt *et al.* 1945a). Hill (1948) states his belief that the appearance of slow waves depends on active involvement of nerve cells. Aring (1949) in his study of Japanese B encephalitis feels that while the death of neurones is proceeding the EEG is abnormal, but when the process is arrested there is a return to normal brain wave rhythms. Such a restitution has been noted in successfully treated neurosyphilis (Callaway *et al.* 1945; Seeley *et al.* 1953). Here is another unsettled question which requires further elucidation.

Our data cannot answer all of the issues raised thus far, but we can say that etiology does not seem the important factor. Regardless of disease process (see table II), where dementia was present EEG changes were noted and in proportion to the degree of dementia. Thus presence and degree of dementia appears to be a more pertinent clinical factor than type of disease process or its rate and nature of progress. This is supported by other studies (Hoch *et al.* 1941; Liberson *et al.* 1945; Mundy-Castle *et al.* 1954; Strauss 1944; Strauss *et al.* 1948; Stroller 1949; Yeager *et al.* 1937).

A final matter to consider is the relevance of psychotic manifestations complicating dementia. Not everyone who becomes demented develops accompanying psychotic trends. By the latter we have in mind major disturbances of behavior, mood and/or thought content ordinarily associated with schizophrenic or affective psychoses. We have felt from our experience that psychosis uncomplicated by dementia (or convulsive disorder) does not produce a significant incidence of EEG abnormalities. This view has been recently substantiated by Lyketsos and associates (1953). We divided our patients into two groups to examine this further — dementia with psychosis and dementia without psychosis. Fifty of our patients fell in the former category, and 21 had no such psychotic complications. Most of the psychotic group were depressed and a few had paranoid trends, although none were typically schizophrenic. Of the non-psychotic groups 17 out of 21 had abnormal EEGs (81 per cent), and of the psychotic group 38 out of 50 had abnormal EEGs (76 per cent). There appears to be no significant difference in *incidence of abnormality* in between these two groups. On statistical evaluation (see table III) of correlation between degree of dementia and degree of EEG change, there is significance (chi-square) only in the non-psychotic group. This being the smaller of the two groups indicates the necessity for larger sampling of non-psychotic demented patients in future studies. The preponderance of psychotic patients in our series is occasioned by our working on a psychiatric service. However, we

must add that because of this we categorized many patients as psychotic who might have gone unnoticed or considered not psychotic by non-psychiatric personnel using less exacting criteria. Another consideration here is the possibility that certain psychotic manifestations (especially depressive) may be mistaken for signs of dementia (psychomotor retardation, e.g.). We discuss this possibility at the conclusion of this paper. These somewhat ambiguous issues would have significant effect on the outcome of data, depending on how they were decided.

Finally we might mention the 16 demented patients who had normal EEGs. Why do they have normal records even though demented ? We cannot answer this completely; we can only offer some tentative explanations; of the 16 patients in this category, 8 had only minimal dementia and another 6 had moderate dementia. It would appear from examination of the entire group of minimal dementia patients (see Results) that only half of these can be expected to have abnormal EEGs. This could be a partial explanation of the incidence of normal EEGs in these 16 patients; although it leaves unanswered the question why the 6 patients with moderate dementia had normal brain waves. Another possibility is that some of these patients may have had fast pre-morbid EEGs which have slowed to a ''normal'' frequency; and some may have suffered previous brain damage which was arrested with a return to a normal EEG pattern (Aring 1949). Future studies are indicated with larger sampling and attention focused on such factors as nature of onset and rate of progress of the dementia in order to elucidate this and other unsettled issues we have mentioned.

Aside from the implications thus far raised, another more practical, clinical one should be mentioned. The EEG may be used as another diagnostic tool in assessing those patients presenting a differential diagnostic possibility of dementia (although at this time it cannot be used to differentiate delirium from dementia) and therefore aid in prognosis and therapeutic planning. This is especially pertinent in those patients of middle or late life who present with a sometimes confusing picture of psychotic depression and dementia. It is often difficult to know if their difficulty is primarily related to organic brain disease or a psychogenic disturbance. An EEG may be of help in such a problem, as we have seen a number of such patients who appeared demented but had normal EEGs. Following a course of ECT in such patients and concurrent with the lifting of their depression, the ''demented'' features disappeared. Some investigation has appeared recently in this area (Hall 1952), and a great deal remains to be done, particularly in view of the large number of older people now entering our public mental hospitals.

## SUMMARY AND CONCLUSIONS

1. In 71 patients with dementia of various etiologies, 55 had abnormal EEG records. Of these 52 showed non-focal slow waves, and 3 predominantly fast records.

2. In the overall group of patients, there was a statistically significant relationship ($p < .01$) between the degrees of dementia (operationally defined as progressive involvement of categories of the sensorial examination) and the degree of EEG slowing.

3. The number of demented patients with major disturbances of mood, thought content and behavior, and EEG slowing, was not greater than those who only had uncomplicated sensorial defects, nor could they be differentiated by EEG alone.

4. Regardless of etiology of the dementia, there would appear to have been a statistically significant correlation between clinical evidence of the severity of dementia and EEG slowing.

5. Sixteen of 71 patients had normal EEG records, none of whom had the severest degree of sensorial dislocation.

6. The possible significance of these findings is discussed in the light of previous work.

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# ABNORMAL BRAIN WAVE PATTERNS IN KWASHIORKOR

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For children suffering from malnutrition we use the African term "Kwashiorkor" when a protein deficiency is associated with edema, anemia, wasting of muscles, characteristic skin and hair lesions, mental changes, and often also enlargement of the liver. The skin lesions consist of ulcerations, fissures, desquamation, purple patches best described by Trowell as enamel paint dermatosis, peeling, pellagroid dermatosis and finally, areas of depigmentation. The hair also may become depigmented in patches or scanty, brittle and dry. A protein deficiency seems to be the common factor in all the cases, although in individual ones additional vitamin deficiencies like keratomalacia, Bitot's spots, angular stomatitis and scrotal dermatosis complicate the picture.

Kwashiorkor, in the language used on the Gold Coast, means a displaced child, implying that the unborn baby would kill the older sibling, possibly by poisoning the milk, so that weaning becomes a necessity. The former translation: "red haired boy", proved to be erroneous. Kwashiorkor is most common during the weaning period and among one and two year old infants, who still are offered the breast and find comfort in sucking but do not get enough milk or any milk at all. No other form of protein is given to replace the missing milk. The problems of protein malnutrition in the tropical zones of Africa, America, and Asia are similar. In Germany, Czerny and Keller used the term "Mehlnährschaden", indicating an unbalanced diet limited to carbohydrates.

In their monograph on kwashiorkor, Trowell, Davies, and Dean have justified their use of the fashionable name of kwashiorkor for this disease as old as mankind. The common pathological findings in addition to the dermatosis are a fatty liver and atrophy accompanied by a lack of enzymes, changes in the heart, kidneys and endocrine glands. Suprarenal hemorrhages in kwashiorkor have been observed in Ceylon by C. C. de Silva, also by Trowell in Uganda and Gillman in Johannesburg.

The brain often appears to be normal at autopsy. Davies writes: "Changes in the brain have not been made the subject of special study and it is not known if there is any histological counterpart to the striking mental changes."

The mental changes, irritability and constant misery on the one hand and hopeless apathy and lack of expression on the other, impressed me deeply upon my arrival in the tropics, and induced me to undertake the present study. Trowell gives an excellent description of these children, who are not comatose except in the terminal state:

"Even those children who are not severely ill are remarkably silent and still. They sit where they are put, and although they may be well able to walk, never seem to want to do so. They have lost all the normal curiosity and desire for exploration that is natural to a child. If their general condition is worse, they are hopelessly apathetic. They lie in wet and dirty beds without protest. They resent any disturbance with an intensity that makes them come suddenly alive; they cry if they are strong enough, or moan if they are weak. A renewal of interest is one of the most obvious signs of improvement and the child who smiles is well on the way to recovery."

## METHOD

All children admitted to the Children's Hospital with the symptoms of kwashiorkor were subject to an EEG study with the exception of those whose condition was too poor to risk transportation to the EEG laboratory.

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An eight channel Ediswan Electroencephalograph was used.[1]

Four pairs of silver cup electrodes (frontal, temporal, parietal and occipital) and a ground electrode were attached to the scalp with collodion and bipolar leads applied for registration.

None of the children were in a comatose or unconscious state. No sedatives were given. Consequently, long stretches of recordings were marred by muscular artefacts. If spontaneous sleep occurred the child was awakened. Hypoglycemia was avoided by feeding before the recording. Some children were able to sit up and feed themselves. Others had to be fed orange juice or milk by bottle.

When the edema subsided and the skin lesions began to heal, a follow-up study was undertaken using the same technique. By this time most of the children were able to sit up and feed themselves. However, approximately one fourth of them did not survive the critical period. Between July and December 1955, twenty-five children with kwashiorkor had brain wave recordings made at the Children's Hospital in Colombo.

TABLE I

AGE, SEX, AND DEATHS AMONG CHILDREN WITH KWASHIORKOR EXAMINED BY EEG

| *Age* | *Number* | *Boys* | *Girls* | *Died* |
|---|---|---|---|---|
| Under 1 year | 1 | — | 1 | — |
| 1-2 years | 7 | 3 | 4 | 2 |
| 2-3 years | 8 | 2 | 6 | 2 |
| 3-4 years | 5 | 2 | 3 | 2 |
| 4-5 years | 2 | 1 | 1 | — |
| 5 years | 2 | — | 2 | 1 |
| Total | 25 | 8 | 17 | 7 |

Two thirds were girls, but among the 7 deaths 4 were boys.

Previous studies on protein malnutrition in Ceylon (Silva 1955) showed no predilection for either sex. So, the higher incidence of kwashiorkor in girls among our 25 patients is considered to be accidental.

[1] I am indebted to Mr. Sidney Pocock, electronic engineer under the Colombo Plan, for reconditioning the apparatus.

The interpretation of the EEG recordings was centered on the basic occipital frequency, and — in cases of absence of a dominant rhythm — on the range of frequencies and the comparison with the usual findings of waking records in each corresponding age group (Jasper 1949). The standard normal values for the occipital alpha rhythm in children have been collected by Lindsley (1939), Henry (1944), Gibbs and Gibbs (1950), Grey Walter (1950). Abnormal tracings gain further significance if the electroencephalographic follow-up studies, after clinical improvement, showed improved patterns or even normal tracings.

## RESULTS

Among the 25 children studied, 2 showed a normal brain wave activity consistent with their age group. Both children had the enamel paint dermatosis with purple patches and marked edema, characteristic of kwashiorkor, also underweight, anemia and angular stomatitis.

Lafirr (1-8/12) and Sitha (2-6/12) were able to sit up and stand up and were mentally active. They lacked the miserable apathetic demeanor of the other patients with kwashiorkor. Lafirr for example, refused the bottle and pointed to the mug and fed himself with milk before the test. The dominant occipital frequency in the record of Lafirr was 5 c/sec. with a range of 3-7 c/sec. Sitha's record showed no dominant occipital frequency, but the range from 3-7 c/sec. was considered to be within normal limits. Clinical recovery was rapid and both children were discharged soon because their beds were needed by critically ill newcomers.

A second group, where follow-up studies could not be done, includes the children with kwashiorkor leading to death.

No child in a moribund or comatose condition at the time of hospital admission or EEG recording is included in this series of 7. At the time of the brain wave test they were apathetic but not unapproachable. They were taking their feedings with assistance, responded reasonably to questions or other stimuli.

TABLE II

NORMAL EEG RECORDS IN CHILDREN WITH KWASHIORKOR WHO RECOVERED RAPIDLY.

| *Name Hosp. No.* | *Sex* | *Age Years* | *EEG* | | *Weight lbs. oz.* | *Hb. Gm. per 100cc* | *R.P.C. million per cu. mm* | *Remarks* |
|---|---|---|---|---|---|---|---|---|
| | | | *dominant occipital frequency* | *range cycles per sec.* | | | | |
| Lafirr no. 9695 | male | 1 8/12 | 5 | 3-7 | 17:2½ | 11.5 | 3.57 | enamel paint dermatosis, edema, diarrhea, round worms, glossitis. Able to sit. |
| Sitha no. 9542 | fem. | 2 6/12 | — | 3-7 | 11:13 | 10.0 | 3.13 | edema, discolored hair, pigmentation on buttocks. Active child, able to sit and to stand. |

Weerasena (table III) died suddenly on the same day, as sometimes occurs in kwashiorkor. Besides the symptoms of severe malnutrition, enamel paint dermatosis and edema of the feet, there were also the signs of vitamin A and $B_2$ deficiency present: photophobia and xerophthalmia. The EEG showed no dominant basic occipital frequency. The activity varied from 1-4 c/sec. Death followed two hours later.

Siriawathie died 2, Premadasa 3 days, Piyadasa 4 days after the test. In all 3 cases abnormal slow waves dominated the picture (fig. 1-2). The same was the case with Kitsiri. At the time the EEG was taken, he was able to sit up. His edema, however, increased and he died 13 days later.

Fanzil (2 8/12) died 27 days later with continous diarrhea. Here the record showed a dominance of slow waves of low voltage

TABLE III

ABNORMAL EEG RECORDS IN CHILDREN WHO DID NOT RECOVER FROM KWASHIORKOR.

| *Name Hosp. No.* | *Sex* | *Age Years* | *EEG* | | *Weight lbs. oz.* | *Hb. per 100cc.* | *R.B.C. million per cu. mm* | *Death occurred after days* | *Remarks* |
|---|---|---|---|---|---|---|---|---|---|
| | | | *dominant occipital frequency* | *range cycles per sec.* | | | | | |
| Siriawathie 8246 | fem. | 1 4/12 | 2 - 3 | 1 - 5 | 12:9½ | 5.4 | 1,62 | 2 | Fig. 1 |
| Piyadasa 8251 | male | 1 10/12 | — | 1 - 4 | 14:0 | 10.36 | 3,82 | 4 | Fig. 2 |
| Premadasa 10349 | male | 2 6/12 | — | 2 - 4 | 16:0 | 8.14 | 2,12 | 3 | Shigella flexner |
| Fanzil 9452 | fem. | 2 8/12 | 2 - 3 | 2 - 6 | 11:10 | 11.5 | 3,4 | 27 | diarrhea, ascariasis and trichuriasis |
| Weerasena 8063 | male | 3 | — | 1 - 4 | 18:0 | 7.40 | 2,62 | 2 hours | also xerophthalmia |
| Kitsiri 12758 | male | 3 3/12 | — | 2 - 5 | 20:10 | 5.4 | 1,62 | 13 | able to sit up ankylostoma d. |
| Hansawathie 8695 | fem. | 5 5/12 | — | 3 - 5 | 19:12 | 8.2 | 2,64 | 23 | Fig. 3 |

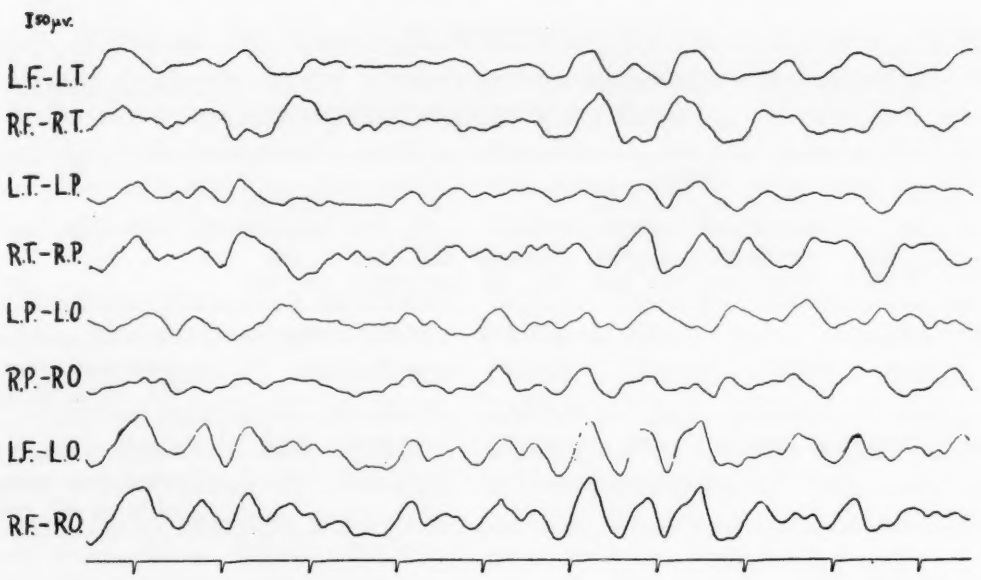


**Fig. 1**

**Siriawathie, female, age 1 1/12, admission no. 8246. Kwashiorkor, died 2 days later.**
**EEG taken on Aug. 19, 1955. The waking record shows mostly 2 to 3 c/sec. slow waves in the occipital leads. The activity varies from 1 to 5 c/sec. Impression: abnormal EEG with activity below the usual range of frequency for this age group.**

type. The range of frequencies varied between 2 and 6 c/sec. superimposed upon by fast activities.

Hansawathie (5 5/12) died 23 days after the test, which showed depressed voltage and activity below the usual range of frequency for her age group (fig. 3).

The third and largest group of the present study of brain wave patterns in kwashiorkor includes the children who recovered from their state of malnutrition. First they lost their edema, then the skin lesions started to heal. At the same time they lost their miserable, apathetic demeanor.

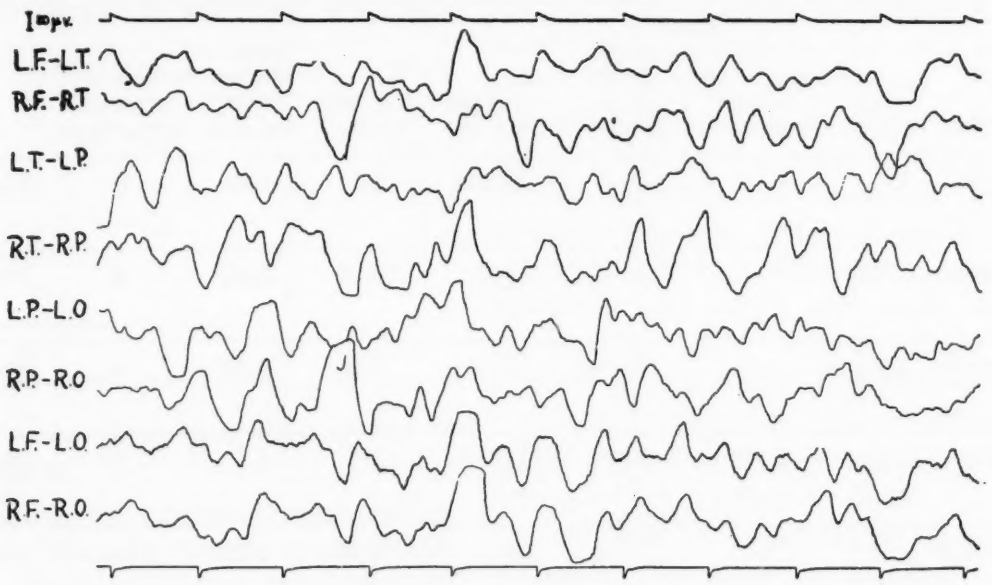


Fig. 2

Piyadasa, male, age 1 10/12, admission no. 11340. Purple patches, depigmented and scattered hair. Diarrhea, angular stomatitis, glossitis, edema since 4 days. Trichuris +. The patient died on Nov. 6, 1955 under signs of general edema and ulcerations.
EEG taken on Nov. 2 awake. No dominant occipital frequency is present. The activity varies between 1 and 4 c/sec., but most waves are 2-3 c/sec. Impression: abnormal records with activity below the usual range of frequency for this age group.

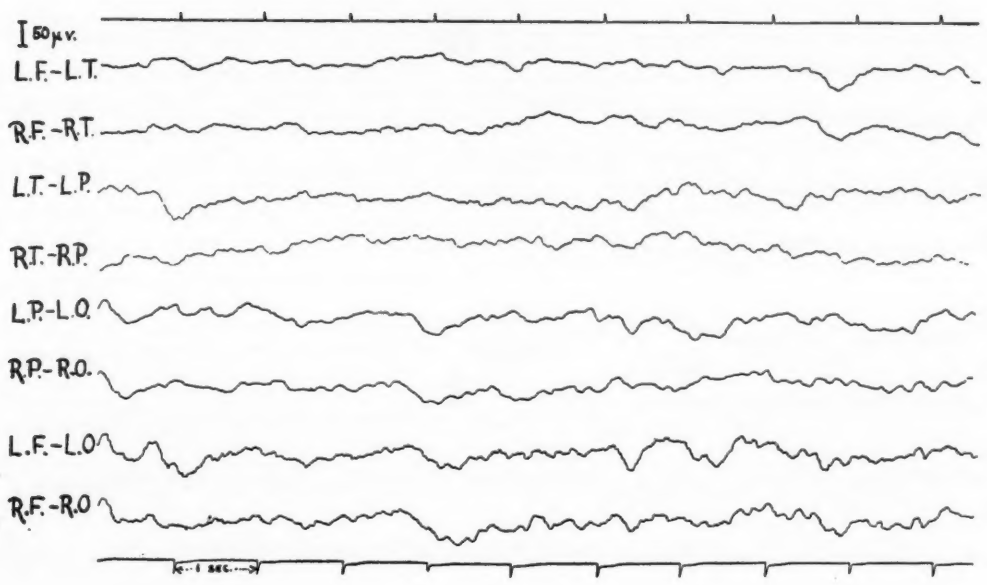


Fig. 3

Hansawathie, female, age, 5 5/12, admission no. 8695.

Kwashiorkor, hemorrhagic rash. Smoky cornea, Bitot's spots.

The patient died on Sept. 18, 1955.

EEG taken on Aug. 26, 1955. The waking record is of low voltage type and shows no dominant occipital frequency. The activity varies between 3 and 5 c/sec. During drowsiness parietal humps and occasional 14 c/sec. spindles are seen over both hemispheres.

Impression: abnormal record during wakefulness with activity below the usual range of frequency and voltage.

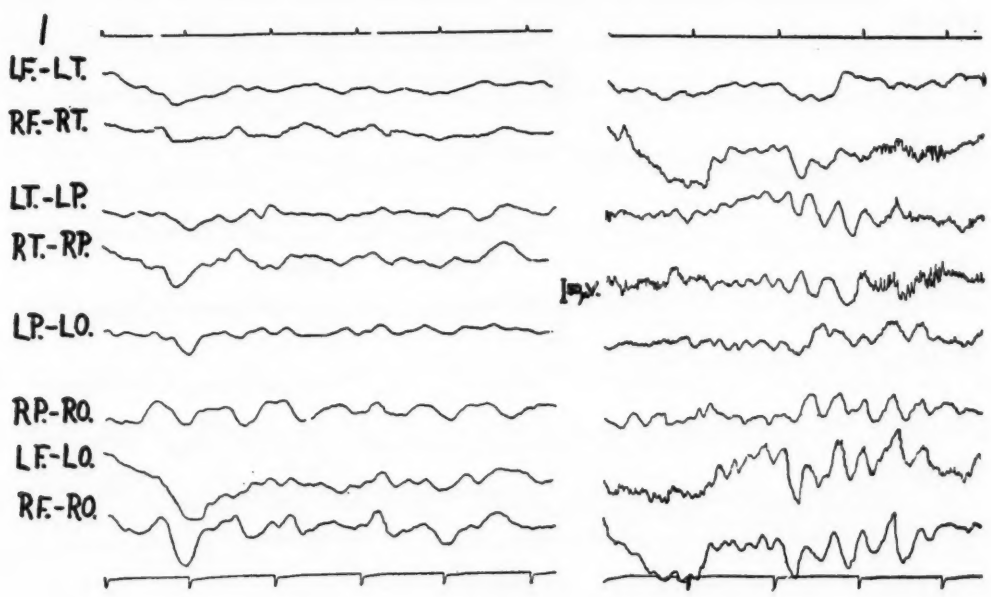


Fig. 4

Karunadasa, age 1, male. Kwashiorkor complicated by vomiting and ascariasis. Admission no. 7432.

EEG taken on July 29, 1955 shows no dominant occipital frequency. The activity varies between 1 and 5 c/sec. 2 c/sec. waves are most common.

Impression: abnormal EEG with activity below the usual range of frequency during the waking state in this age group.

EEG taken on August 17, 1955 shows a marked improvement. Still no dominant occipital frequency is present. Moving artifacts mar the record. The activity varies from 3 to 6 c/sec. The previously described 2/sec. waves are absent.

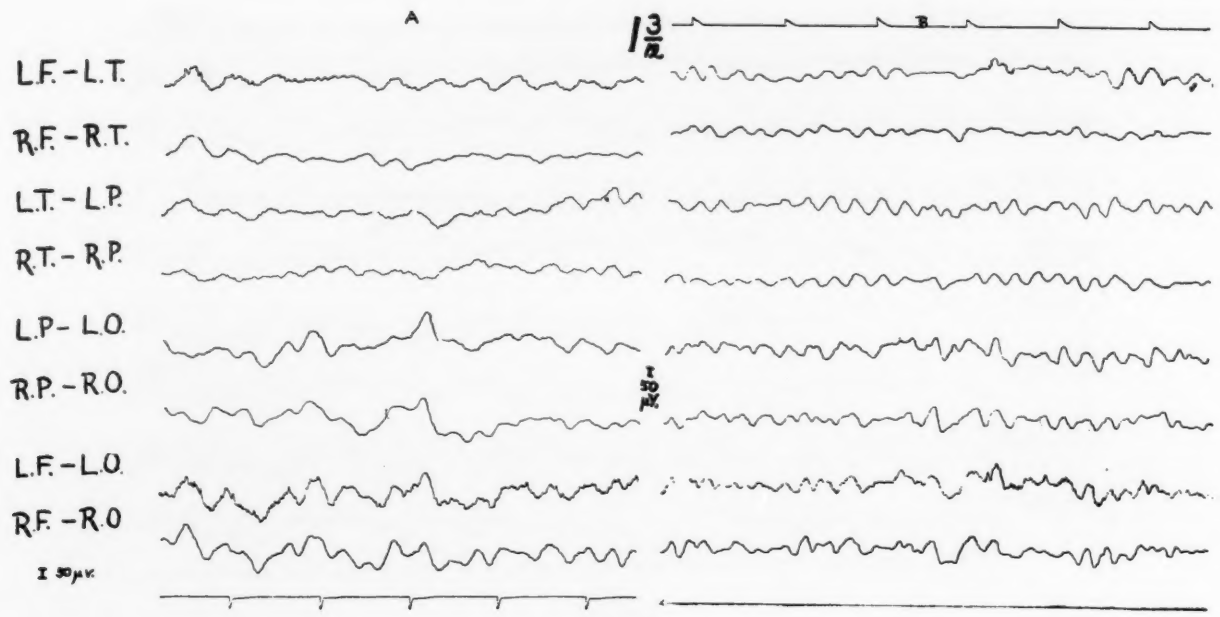


Fig. 5

Ajaran Bee, age 1 3/12, female, admission no. 7750.
Diagnosis: Kwashiorkor, infection with Shigella flexner + virchow.
On admission the child was irritable. Good recovery after one month.
A. EEG taken on Aug. 8, 1955 during wakefulness shows no dominant occipital frequency. The activity varies between 2 and 4 c/sec. Impression: activity below the usual range of frequency for this age group.
B. EEG taken on Sept. 7, 1955 with the child awake. No dominant occipital frequency. The activity varies between 3 and 7 c/sec. Impression: improvement; the record is considered to be within normal limits.

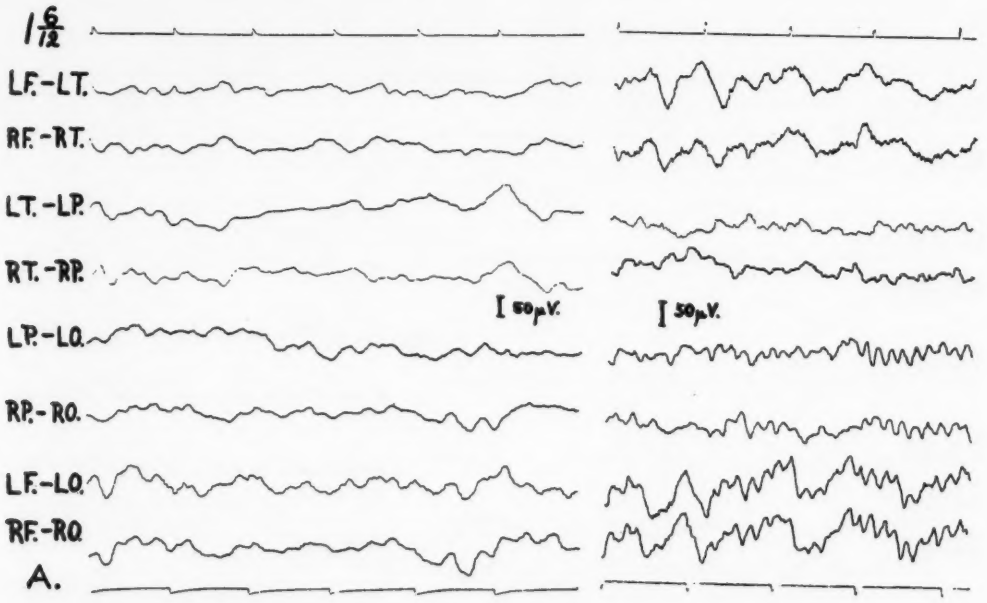


Fig. 6

Amusathulaima, 1 6/12, female. Admission no. 11226.
Edema, enamel paint rash, angular stomatitis, ascariasis.
EEG taken on Oct. 28, 1955. The record is marred by artifacts due to coughing, which preceded the expulsion of an ascaris. The activity is of low voltage type and varies between 2 and 5 c/sec. Three-4 c/sec. waves are most dominant, but there is no constant basic occipital frequency. Impression: abnormal EEG, low voltage type, with activity below the usual range of frequency.
EEG taken on Nov. 29, 1955 when she had lost her edema and her apathy and was able to sit up. The record shows a basic occipital frequency of 6-7 c/sec. interrupted by some 4-5 c/sec. activity and occasional slow waves. Impression: normal EEG for this age group.

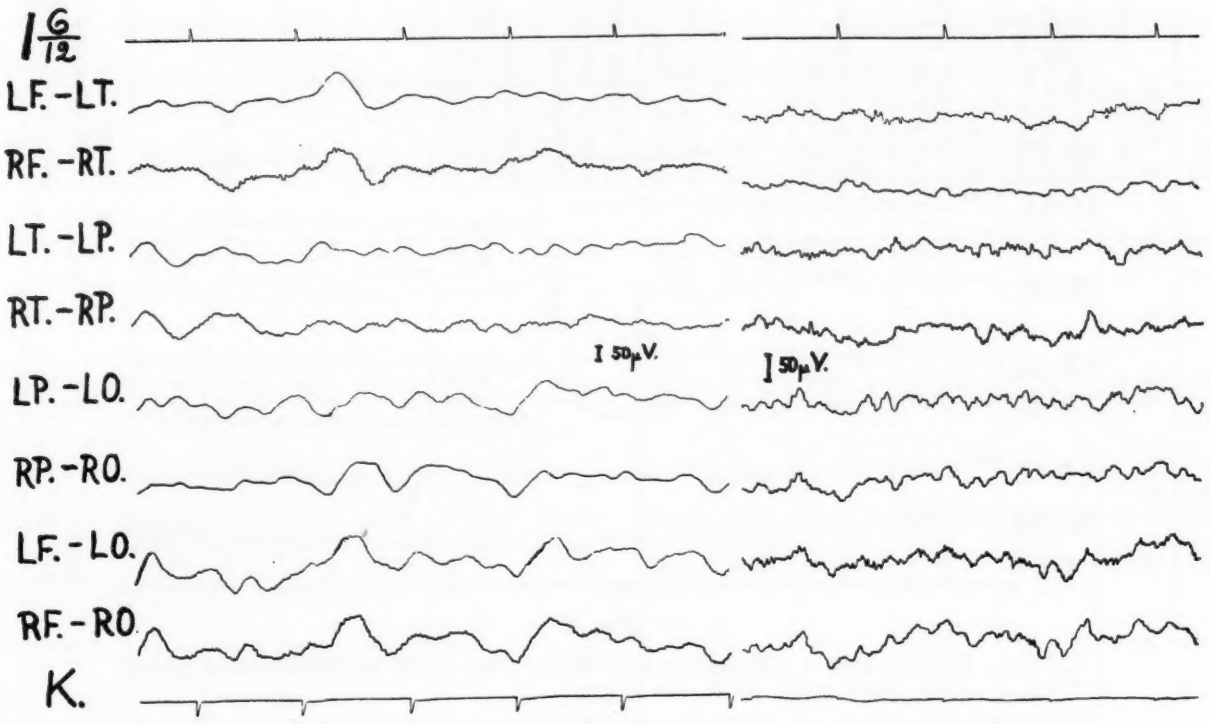


**Fig. 7**

Kusumawathie, female, age 1 6/12, admission no. 8251. Kwashiorkor, ascariasis, trichuriasis, persistent irritability.
EEG taken on Aug. 19, 1955. The dominant occipital activity varies between 2 and 3 c/sec. with occasional 1-4 c/sec. waves. Impression: Abnormal record with activity below the usual range of frequency.
EEG taken on Sept. 6, 1955 shows no dominant occipital frequency. The activity varies from 3-7 c/sec. superimposed upon by fast activity. Comparison with the previous record shows the absence of the very slow waves and return to normal frequencies.

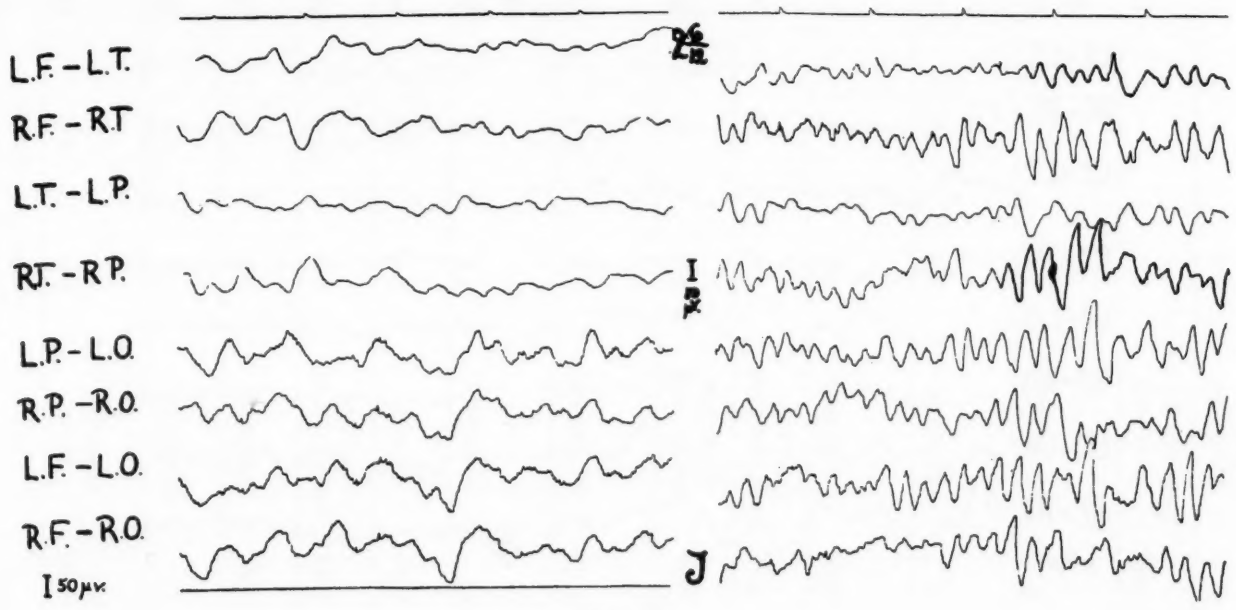


**Fig. 8**

Jayanpathie, age 2 6/12, female, admission no. 9769. The child is in constant misery, but capable of sitting up. General edema, enamel paint dermatosis, wasting.
EEG taken on Sept. 28, 1955 during wakefulness. The record shows no dominant basic occipital frequency. The activity varies between 2 and 4 c/sec., superimposed upon by 30 c/sec. waves. Impression: abnormal EEG with activity below the usual range of frequency for this age group.
EEG taken on Oct. 14, 1955. The child has lost her edema. During the recording she is very quiet, but keeps her eyes open. The activity varies between 4 and 6 c/sec. Comparison with the previous record shows marked improvement.

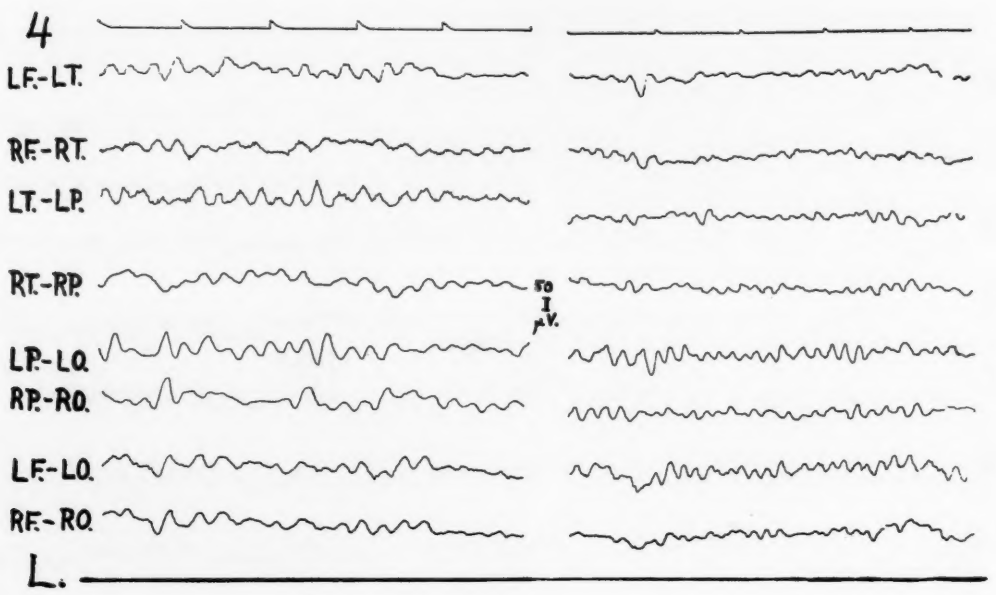


Fig. 9

Lalitha, female, age 4, admission no. 9311. The child is listless and quiet. Pitting edema and rash of lower limbs.

EEG taken on Sept. 9, 1955 shows a basic occipital frequency of 4 c/sec. interrupted by 2-3 c/sec. waves in the waking record.

Impression: abnormal EEG with activity below the usual range of frequency for this age group.

EEG taken on Sept. 22, 1955 shows a basic occipital frequency of 5-7 c/sec. and a return to normal.

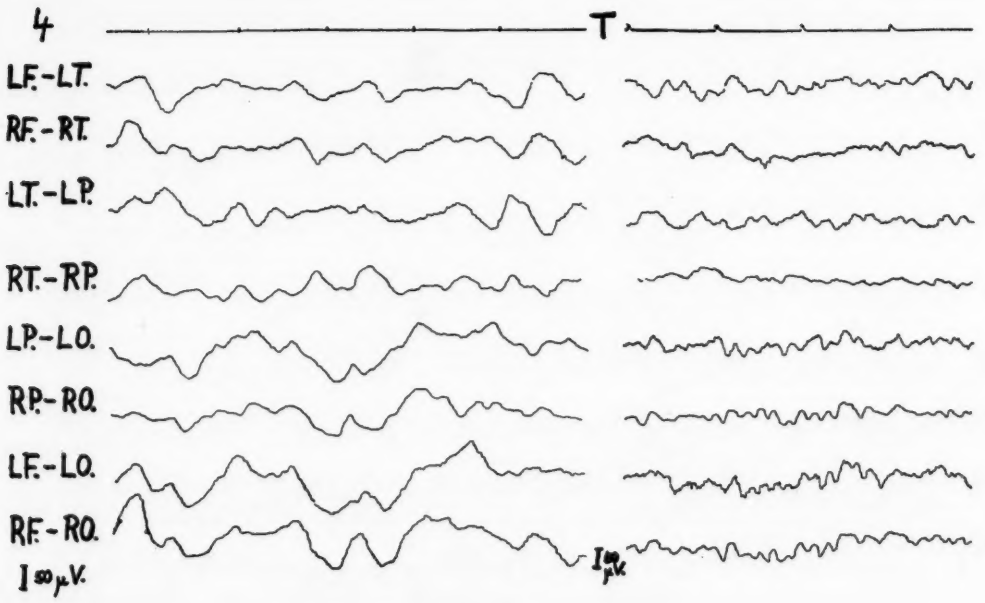


Fig. 10

Trelor, male, age 4, admission no. 10314.

Malnutrition, edema, depigmentation, diarrhea, in constant misery.

EEG taken on Oct. 5 shows many artifacts due to coughing. No dominant occipital frequency is present. The activity varies from 2 to 6 c/sec. The slow waves dominate the tracing. Impression: abnormal EEG with activity below the usual range of frequency for this age group.

EEG taken on Oct. 21, 1955 shows a marked improvement in comparison to the previous record. The activity varies from 4 to 7 c/sec.

TABLE IV DATA OF CHILDREN RECOVERING FROM KWASHIORKOR BEFORE AND AFTER TREATMENT.

| | | | I. UPon ADMISSION | | | II. FOLLOW-UP | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Name, Sex Hospital number 1955* | *Age years* | *Mental status* | *EEG range of frequency c./sec.* | *dominant occipital frequency c./sec.* | *Time elapsed (days)* | *EEG range of frequency c./sec.* | *dominant occipital frequency c./sec.* | | *Weight lb.:oz.* | *hb. Gm per 100 cu. cm.* | *R.B.C. in millions* | *Remarks* |
| Sriyawathie, girl 11122 | 10/12 | very irritable | 2-5 | 3-4 | 36 | 3-6 | 4-6 | I<br>II | 15: 5<br>13:11 | 10.5<br>8.6 | 3.01<br>2.62 | Severe edema, Bitot's spots xerophthalmia, angular stomatis. |
| Karunadasa, boy 7432 | 1 | apathetic | 1-5 | — | 19 | 3-6 | — | I<br>II | 11:10<br>13: 9 | 6.8<br>7.4 | 2.04<br>2.47 | Fig. 4. |
| Arajan Bee, girl 7750 | 1 3/12 | irritable | 2-4 | — | 30 | 3-7 | — | I<br>II | 12: 1<br>13:13 | 9.2<br>9.2 | 3.18<br>3.12 | Fig. 5. |
| Amusathulaima, girl 11226 | 1 6/12 | unable to sit irritable | 2-5 | 3-4 | 30 | 4-7 | 6-7 | I<br>II | 14: 7<br>15: 8 | 10.0<br>11.8 | 3.02<br>3.84 | Fig. 6. |
| Kusumawathie, girl 8251 | 1 6/12 | irritable | 1-4 | 2-3 | 18 | 3-7 | — | I<br>II | 15: 2<br>14: 8½ | 7.4<br>9.2 | 2.48<br>2.89 | Fig. 7 |
| Bindi, girl 8698 | 2 | apathetic | 3-5 | 4 | 100 | 4-8 | 6-8 | I<br>II | 14: 5<br>18:11 | 7.0<br>8.4 | 2.02<br>3.02 | Kwashiorkor and keratomalacia complicated by chicken pox. |
| Rupawathie, girl 6696 | 2 6/12 | apathetic | 2-7 | 2-3 | 58 | 2-8 | 4-5 | I<br>II | 9: 0<br>13: 1 | 7.4<br>8.9 | 2.67<br>2.91 | Kwashiorkor and keratomalacia loss of vision, mental retardation. |
| Mohideen, boy 10251 | 2 6/12 | morose and irritable | 2-5 | — | 9 | 4-7 | — | I<br>II | 14: 8<br>14:11 | 7.0<br>8.2 | 2.85<br>2.64 | Passed 200 roundworms, also trichuriasis. |
| Jayanpathie, girl 9769 | 2 6/12 | in constant misery | 2-4 | — | 16 | 4-6 | — | I<br>II | 16: 2<br>16: 0 | 6.7<br>7.4 | 2.98<br>2.02 | Fig. 8. |
| Sorajanie, girl 7948 | 2 8/12 | apathetic | 2-5 | — | 33 | 4-8 | 6-7 | I<br>II | 15: 1½<br>15:15 | 7.2<br>9.6 | 2.24<br>2.51 | Kwashiorkor complicated by tbc. pulm and Salm. virchow. |
| Premawathie, girl 9981 | 3 | irritable | 2-5 | — | 25 | 4-8 | — | I<br>II | 16:13<br>16: 5 | 7.0<br>7.4 | 2.81<br>2.26 | Bitot's spots, corneal ulcer ascariasis, trichuriasis, ankylost. |
| Swarnalatha, girl 10989 | 3 | able to sit up | 2-6 | — | 23 | 4-8 | 7 | I<br>II | 18: 0<br>21: 0 | 9.2<br>7.0 | 2.88<br>2.14 | Bitot's spots, gutter syndrome angular stomatitis; Salm. virchow. |
| Nandawathie, girl 12608 | 3 4/12 | in misery does not sit up | 2-7 | — | 19 | 2-9 | 9 | I<br>II | 22: 3<br>19: 1½ | 5.0<br>5.9 | 1.46<br>1.83 | Angular stomatitis ulcer on scalp. |
| Lalitha, girl 9311 | 4 | apathetic listless | 2-6 | 4 | 13 | 5-7 | 7 | I<br>II | 16: 5½<br>15:12½ | 10.8<br>8.9 | 3.37<br>3.07 | Fig. 9. |
| Trelor, boy 10314 | 4 | miserable | 2-6 | — | 16 | 4-7 | — | I<br>II | 21: 0<br>20: 4 | 7.4<br>8.9 | 2.16<br>2.97 | Fig. 10. |
| Piyaseeli, girl 10556 | 5 | able to sit up | 2-6 | — | 23 | 4-8 | — | I<br>II | 20:14<br>22: 9 | 11.8<br>5.2 | 3.48<br>1.64 | Fig. 11. |

Table IV gives a comparative picture of the EEG findings in this group of 16. The tabulation is arranged according to the age of the patient. With the exception of the 2 children mentioned before, whose EEG was within normal limits a few days after admission to the hospital, all waking records were abnormal with activity below the usual range of frequency. In many cases a dominant occipital frequency was obviously absent. Slow waves between 2-4 c/sec. were most marked even in those instances in which the range of frequencies included the 6 and 7 c/sec. band.

A follow-up study was done after the child had regained his mental alertness. The number of days that elapsed between the first and second EEG is indicated in column 7 of table IV. When the second EEG was done the child was able to sit up and feed himself. The EEG showed a definite improvement in every single one of the surviving patients and a return to normal during the time of observation in 12 out of 16, long before the anemia responded to treatment. It was felt, that a prolonged period of observation would have brought on complete normalization in most of these children. Because of the shortage of beds and the necessity of admiting more critically ill children to the hospital, convalescent patients had to be sent home.

In every case the values for weight, hemoglobin and red cell count indicate a severe damage to the organism by malnutrition and accompanying diseases. At the time of apparent normalization of the brain wave pattern, weight and hemoglobin level were still markedly subnormal.

Eight examples of tracings of children recovering from kwashiorkor before and after treatment are presented in figures 4-11.

In two instances, however, repeated follow-up studies failed to demonstrate a return to normality. Rupawathie (2 6/12) who also suffered from severe keratomalacia with blindness, continued to have a pattern with marked slow waves and signs of mental retardation and lack of activity. Premawathie (3)

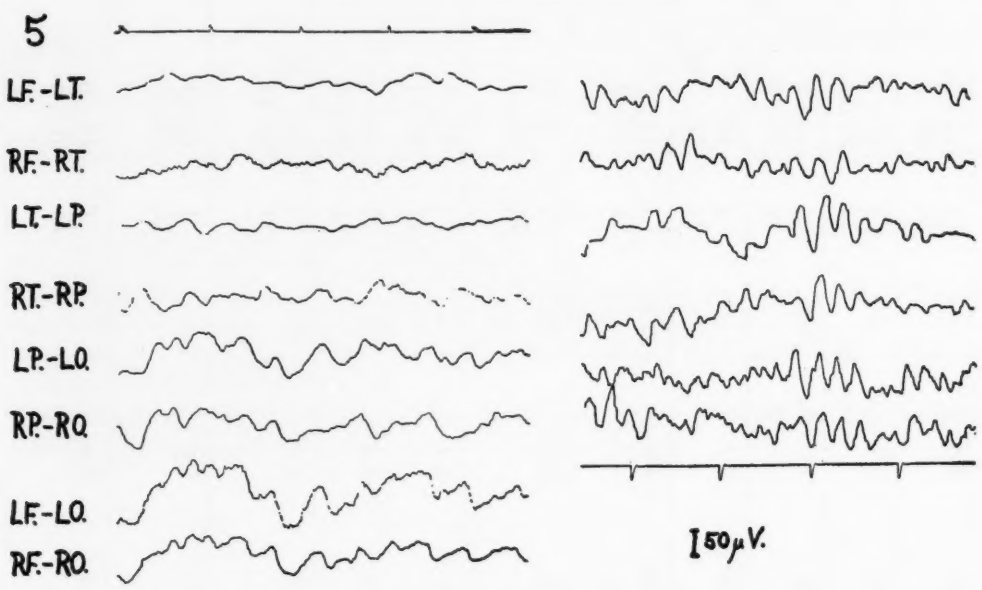


Fig. 11

Piyaseeli, female, age 5, admission no. 10556.
Kwashiorkor, keratomalacia, corneal ulcer, Bitot's spots, prolapse of rectum, ascariasis, trichuriasis.
EEG taken on Oct. 17, 1955 shows many muscular artifacts due to movements. No dominant occipital frequency is present. The activity varies from 2 to 6 c/sec.
Impression: abnormal EEG with activity below the usual range of frequency for this age group.
EEG taken on Nov. 9, 1955 after marked clinical improvement. The patient is able to walk, edema and corneal ulcer have healed. The activity varies between 4 and 8 c/sec.

was also affected by Vitamin A deficiency (nyctalopia, Bitot's spots) and in addition was infested with roundworm, hookworm and Salmonella virchow, and was not able to stand alone when the last test was carried out. In both cases of kwashiorkor with additional vitamin deficiencies and with hookworm anemia in the latter, permanent brain damage must be considered.

## DISCUSSION

It is obvious, that the damage from malnutrition not only affects the skin and the internal organs; the function of the cerebral cortex is also affected, clinically recognizable by prevalence of slow waves below the usual frequency in the respective age groups. Choremis and Nestoridou (1954) reported EEG abnormalities in "toxicosis" of infants due to alimentary origin. Their patients were comatose on admission and some of them showed a paralytic type of respiration. The EEG changes rapidly became normal after recovery from the disease. The observations of the Greek authors are made on a different level. Any coma no matter what the cause, may be associated with high voltage slow waves or voltage depression. In our series of children with kwashiorkor no comatose state was present at the time of the EEG recording.

Hypoglycemia can be excluded as unlikely because of the correct timing of food intake before recording. Severe anemia, however, might be a contributory factor causing anoxia in sensitive brain cells.

The mental state was depressed or at least disturbed in all cases with abnormal records containing an unusually high percentage of slow waves. After clinical improvement and mental recovery, the EEG pattern became normal in most cases. Only exceptionally, the altered functional state remained irreversible. In those who survived, the electroencephalographic frequencies returned to normal findings long before red cell and hemoglobin levels improved. Anemia, therefore, is not the most important factor causing the abundance of slow waves.

In normal children it would be a misconception to think that the slow waves of early childhood simply change to 8-12 c/sec. frequencies as the central nervous system becomes more stable and differentiated. The slow waves continue but they are less dominant and are masked by more prominent 7-12 c/sec. frequencies. The slow waves regain their dominance in sleep and under many pathological conditions. Among these is kwashiorkor. With the mental apathy and misery in mind, it is not surprising to observe the functional changes also in the brain wave pattern. Is unexplained sudden death in kwashiorkor the result of impaired brain function ?

The pathological EEG findings on admission of the cases of kwashiorkor give no clue as to whether the child will recover or succumb. Slow waves and very slow waves occur in both instances.

## SUMMARY

1. Electroencephalographic tracings were done on 25 children with kwashiorkor. Coincident with the symptoms (enamel paint dermatosis, depigmentation, edema, mental apathy or constant misery) the brain wave tracings were as a rule abnormal with activity below the usual range of frequency considering each age group (8 months to 5 years). Two children, who showed normal mental response and were able to sit up on admission, had normal EEG records.

2. In 7 patients who did not survive, the EEG was taken before a comatose state developed. It showed a preponderance of 1-3 c/sec. slow waves, but absence of a dominant basic occipital frequency in most cases. The range varied between 1-6 c/sec.

3. Most children recovered following administration of a high protein diet and vitamins. On admission, their brain wave pattern was not significantly different from that of the fatalities. Upon recovery, when the edema and the skin lesions had disappeared and the children were able to sit up, the EEG was found to be within normal limits in spite of persisting anemia.

4. In 2 cases of kwashiorkor and vitamin deficiency repeated follow-up studies failed to show complete normalization. The possibility of a permanent brain damage due to malnutrition must be considered.

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# CLINICAL AND LABORATORY NOTES

Editor for Western Hemisphere and Far East, R. S. SCHWAB, M.D., Boston, U.S.A.
Editor for Europe and Middle East, F. BUCHTHAL, M.D., Copenhagen, Denmark

## RECORDING THE FOURTEEN AND SIX PER SECOND SPIKE PHENOMENON

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(Received for publication: May 16, 1955)

Fourteen and 6 per sec. positive spikes have been observed during drowsiness and sleep in 32 of 1600 patients studied in the past six years. There were 720 of these recordings which were considered to have shown various abnormalities in the entire series. Thus 4.4 per cent of patients with abnormal electroencephalograms, and 2 per cent of the entire series have been reported to manifest 14 and/or 6 per sec. positive spike dysrhythmia. Such spikes have been reported to be distorted forms of normal sleep patterns which have been shown in animals to originate in the thalamus and hypothalamus (Gibbs and Gibbs 1951, 1952). However, Hill (1953) has stated: ''The inclusion of 14 and 6/sec. positive spikes is surely only justified by the rigidity of the technique, and must be criticized as artifacts of the method.'' We assume this statement implies the polarity of such spikes as being questionable, therefore careful evaluation of 12 such patients was undertaken.

### METHOD

An eight channel Grass instrument was used, recording monopolar and bipolar methods simultaneously. As the 14 and 6 per cent spikes appear maximal in temporal and occipital areas of one hemisphere with little if any spread to the adjacent hemisphere, monopolar leads were referred to ear references on the side opposite the discharge (fig. 1) and also to an indifferent noncephalic reference as suggested by Schwab (1951). A separate electrode was used for grounding rather than the ear reference. Bipolar technique included recording from frontal to parietal, parietal to occipital, frontal to temporal, temporal to occipital and parietal to

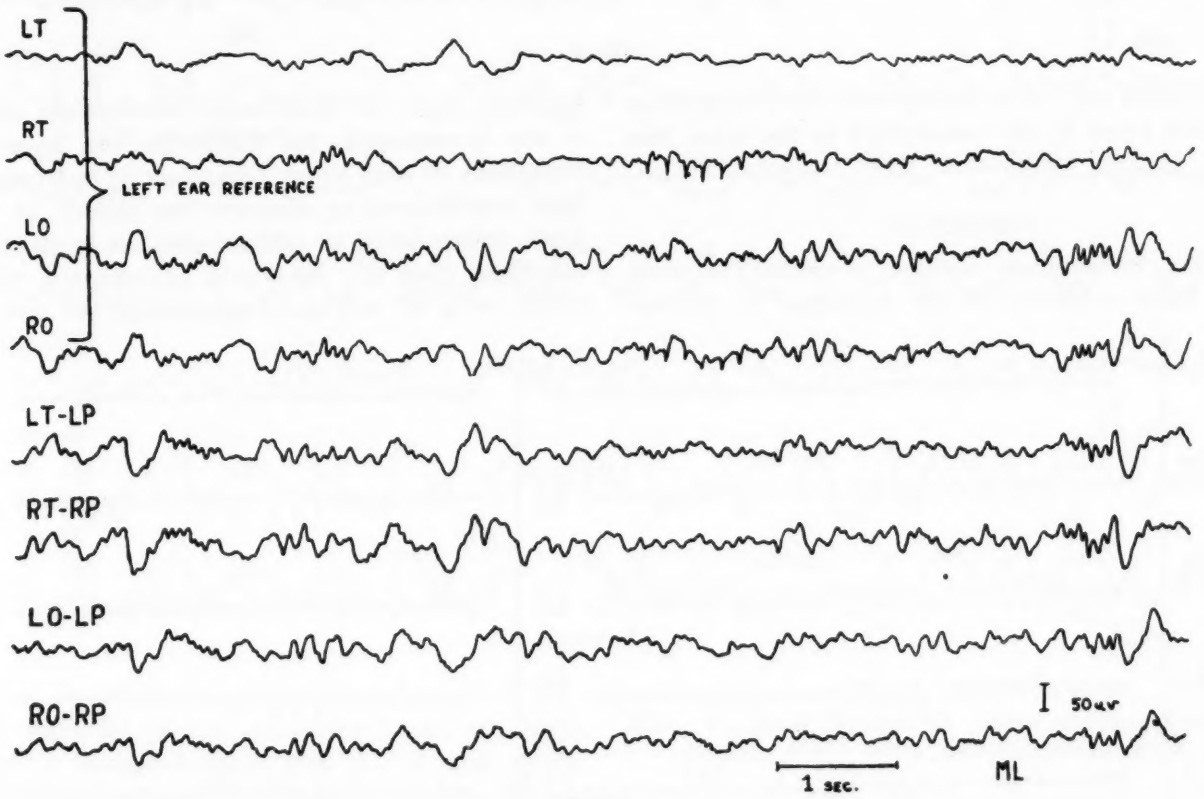


Fig. 1

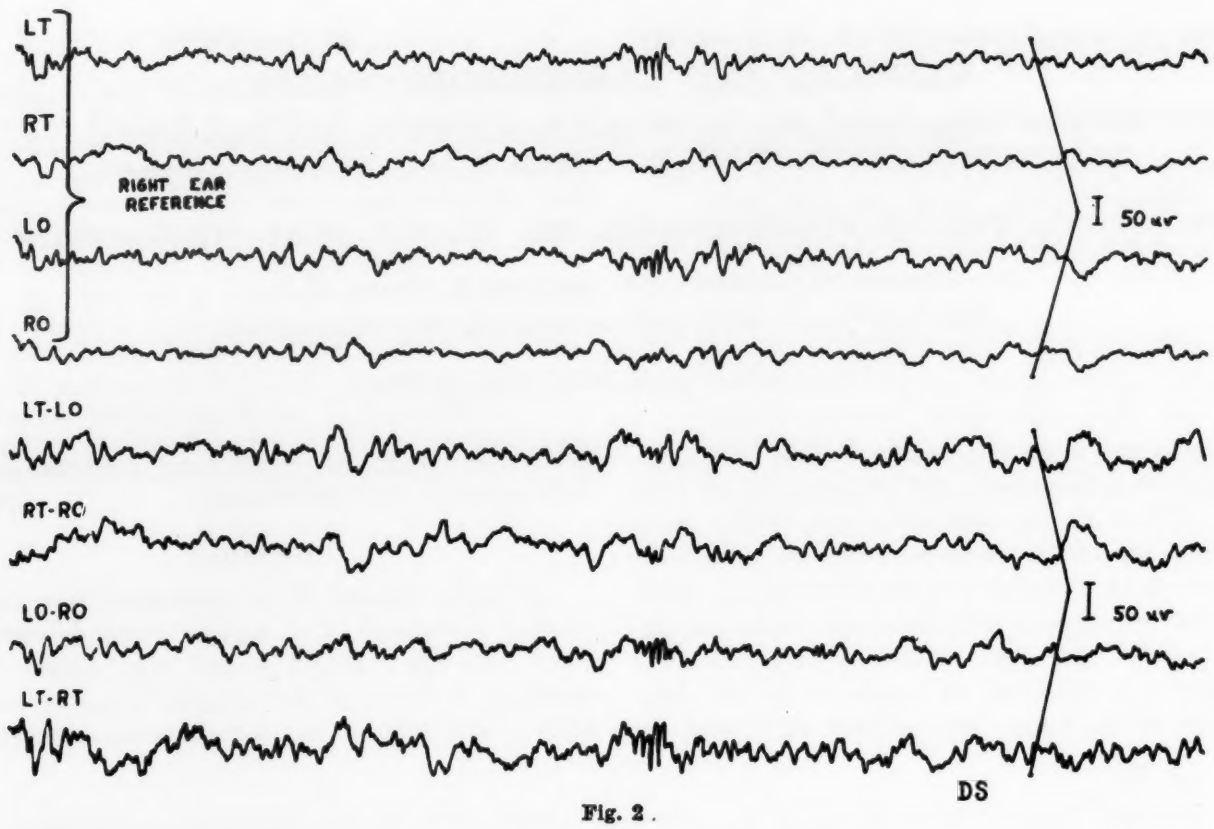


Fig. 2.

temporal areas over each hemisphere. Recording from homologous areas in one hemisphere to the other was included, i.e. left temporal to right temporal, etc.

## FINDINGS

Of the 12 subjects studied, 4 failed to show further EEG evidence of the spiking. In the remainder, when an indifferent non-cephalic reference or ear is employed, the discharges can be noted independent of each other regardless of reference used. This would seem to disprove the theory of 14- and 6/sec. spikes being an artifact peculiar to an active ear reference (fig. 2). As would be expected, when the bursts were of sufficient magnitude the ear on the

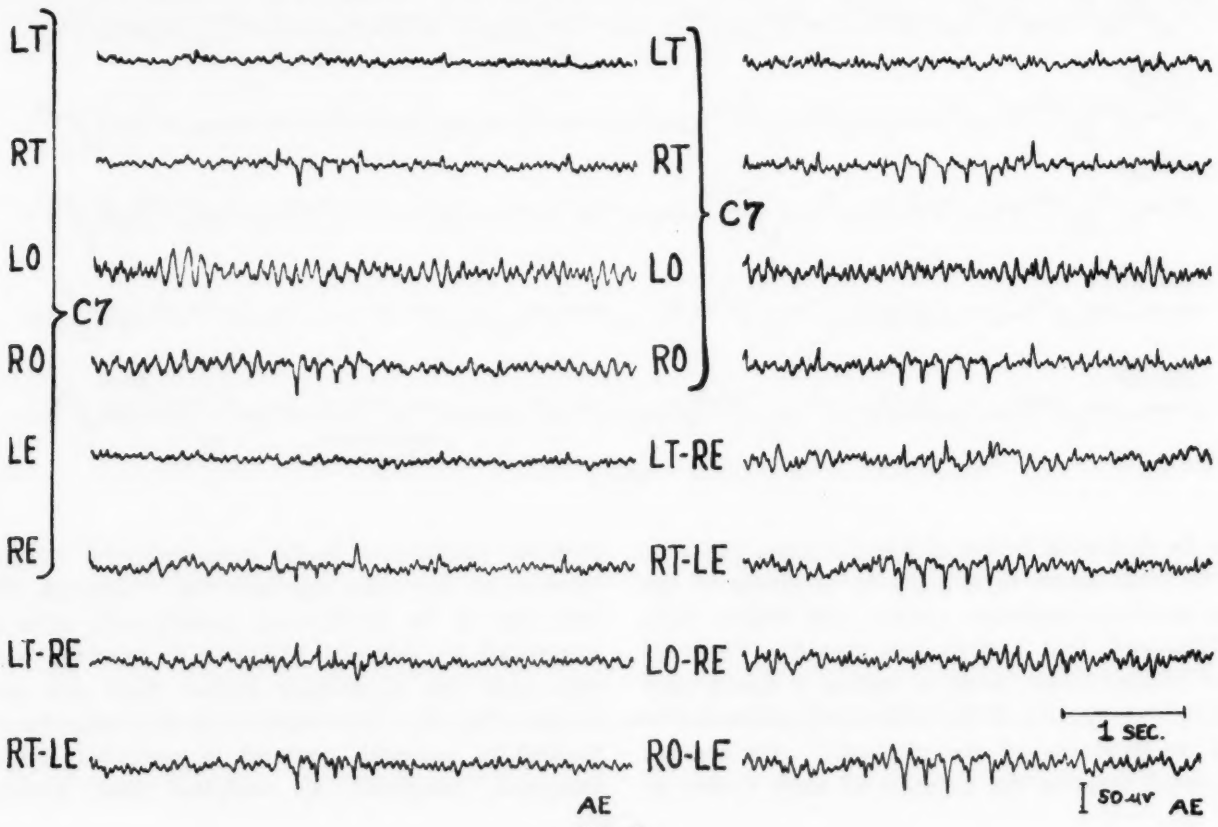


Fig. 3

affected side becomes active driving grid two positive, the spikes then become inverted and appear as negative spikes in leads referred to that ear (fig. 3). The discharge can be recorded using bipolar methods but is subject to certain restrictions. The electrode linkage providing a record of this phenomenon simultaneous with its appearance on the monopolar channels was left temporal to right temporal and to a lesser extent left occipital to right occipital, and frontal to temporal linkages on the side involved. As may be expected, discharges were not recorded when the linkage was otherwise as placing an identical charge upon both grids would tend to cancel out the waves (fig. 1 and 4). If bipolar technique is followed in such a way as to allow the left temporal or occipital leads be placed upon grid 1 and the right temporal or occipital upon grid 2, 14 and 6/sec. negative spikes will result indicating positive spikes in the right hemisphere (with respect to monopolar recording), this is also conversely true (fig. 2 and 4).

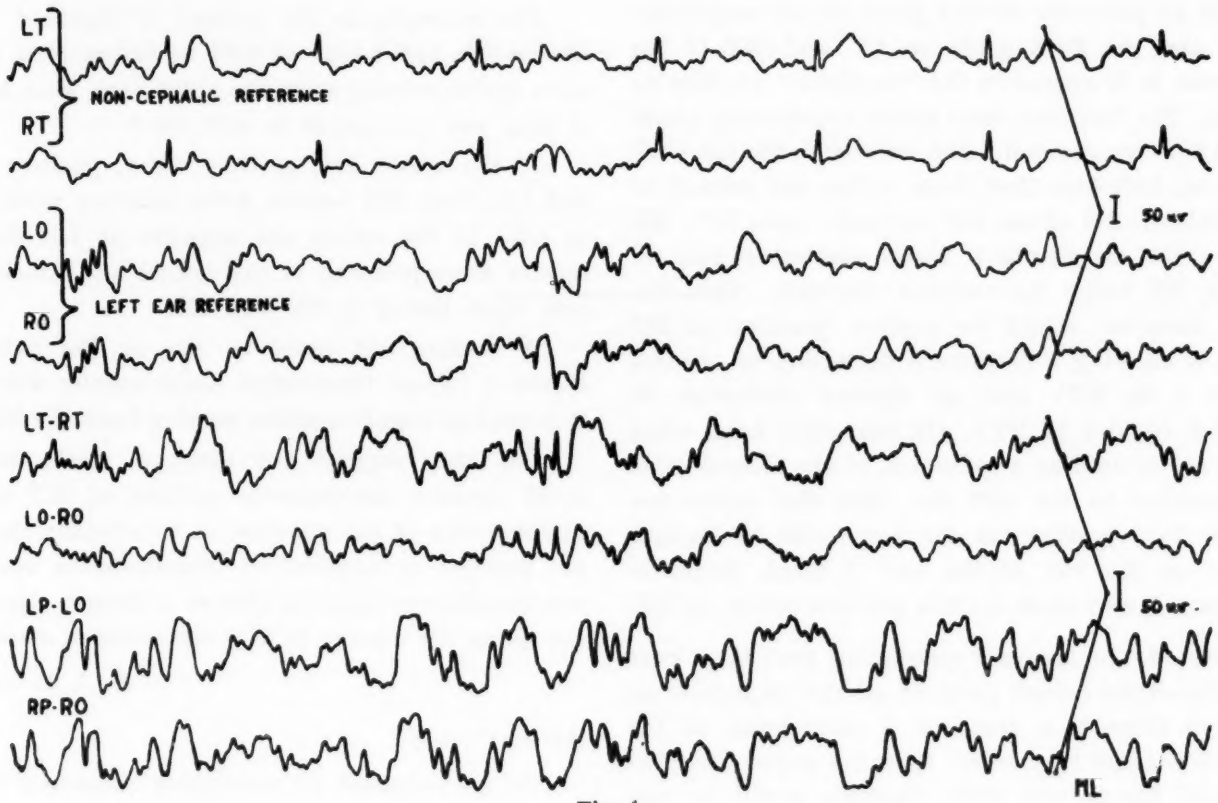


Fig. 4

## CONCLUSIONS

1. The 14 and 6/sec. spikes may best be illustrated in temporal and occipital areas during drowsiness and light sleep when recording by monopolar and bipolar methods.

2. The 14 and 6/sec. spikes assume a positive appearance on the cortex when an indifferent noncephalic reference and bipolar methods are used, in the latter instance they may assume a negative appearance if the active electrode is placed upon grid 2.

3. Regardless of recording method the phenomenon can be recognized by its uniqueness of appearance, thus facilitating its clinical significance which may be evaluated to advantage despite arguments regarding polarity.

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## EDITORIAL COMMENT

There can be no doubt that the spike phenomena shown in these records are there, and in the case of the first 3 I would have no hesitation in accepting them as of cerebral origin. I think that the little discharges in figure 4 are probably of cerebral origin, but less certainly so. I have never been happy about the statement that these spikes are *surface positive.*

The distinction is, of course, of more than academic interest since if these spikes are thought to be surface positive when in fact they are surface negative, it leads to their identification on the wrong side of the head.

*Figure 1.* If the first grids of the amplifiers of the first 4 channels in this figure are connected to the scalp electrodes and the second grids all to the left ear reference, then the spikes records could be surface negative at the left ear electrode. The absence of these spikes in the bipolar records and their specific absence from LT - LP can be explained on their very small size. They are seen in the monopolar recording only in those channels in which the inter-electrode distance is greatest, that is RT and RO.

*Figure 2.* Using the non-cephalic reference it is necessary to place the second grids of the amplifiers on Ref and the first grids on LT and RT if the cardiogram is to appear in the ''upright'' position as recorded. The fact that these spikes are showing phase reversal between channel 2 and channel 5, the LT - RT connection, indicates that these spikes are arising in the neighbourhood of the RT electrode, since LT - RT — RT - Ref constitute a series connected pair of channels, RT being the common electrode. This discharge, however, would be surface positive at RT since it is showing a downward deflection in channel 2 (grid 1 to RT) and an upward deflection in channel 5 (grid 2 to RT). On the other hand when the left ear is used as a reference, if the *second* grids are connected to the left ear, then the spikes are again surface positive on the right side or surface negative on the left at the ear. I think therefore that figure 2 may show surface positive spikes at RT.

*Figure 3.* In figure 3 presuming that they have again placed the second grids of all the amplifiers on Ref (and there is a trace of a cardiogram in the record to suggest they have) then the spikes recorded in second, fourth and sixth channels would be suspected as arising nearer to RT - RO and RE than to other electrodes and since they reverse between these channels and channel 7 (LT - RE) one would suspect them of being surface positive. There is no position recorded to suggest that this is not so. I would, however, add that I have recorded surface positive spike foci by bipolar recording at electrodes where on other occasions surface negative spikes have appeared more frequently. I think the authors may therefore be right. I would, however, agree that simultaneous spiking from different areas of the cortex on the same side makes it very suspicious that the origin of the spikes is nearer to some other reference point.

*Figure 4.* What I have said in respect to figure 1 applies here and it depends upon which grids were connected to the ear reference. In LO - RO and in LT - RT the spikes look as if they are surface negative on the right side. If the *first* grids of the first four channels were connected to the right ear reference, and this is *not* how it is written on the figure, then indeed these spikes could be surface positive on the right; but if the second grids are connected to this right ear reference as written, then the spikes could be negative at the right ear. There is no case for surface positive left sided spikes in either case.

D. H.

They have omitted the crucial test, namely of running simultaneously to each ear (not joined).

For example, in the patient of figure 4 (whose illustration could just as well be interpreted as negative spikes coming from the right ear) what happens if they run monopolar to left ear ?

If the spikes are, as they claim, positive at LT and LO, they will remain down-pointing when linked to LE. If the spikes are negative at LE they will appear down-pointing in the second and fourth channels when linked to RT and RO.

A similar test could be run on the patient of figure 1 (whose illustration could equally well be interpreted as negative spikes coming from the left ear).

Can they suggest any neuronal mechanism that could produce simultaneous spiking at RT and RO (irrespective of the question as to whether the spikes are positive or negative) ? Simultaneous spiking in non-homologous areas is always a danger signal that the spikes are coming in over the common electrode.

M. A. B. B.

*Authors reply* :

In all instances of monopolar recording the reference was placed upon grid two. We agree that simultaneous spiking from different cortical areas should lead one to suspect reference electrode involvement; however, in the case of the phenomenon in question, if a reference were implicated we should also expect to see the activity in other electrodes referred to that reference. This in our experience has never happened, and unfortunately in the effort to limit the number of tracings in this presentation failed to include one pointing this out. This also applies to his (D.H.) remarks upon figures 1 and 4.

We routinely record simultaneously to each ear (not joined), on the same side and opposite sides. We

must disagree with the remarks in sentence three (M.A.B.B.). If the spikes are positive and of sufficient voltage in the LT and LO there would be every reason to expect the left ear to become active; thus referring the LT and LO to the left ear would be placing an identical charge upon both grids and virtual cancellation of the spikes from LT and LO would result, except possibly the recording of negative spikes in electrodes removed from but referred to the left ear.

We do not wish to imply the spikes are of cortical origin, but rather arise from a subcortical mediator peculiar to the temporal-occipital areas.

T. M. G.

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*Reference*: GARNESKI, T. M. and GREEN, J. R. Recording the fourteen and six per second spike phenomenon. *EEG Clin. Neurophysiol.*, **1956**, *8*: 501-505.

# PIGMENTARY RETINAL LIPOID NEURONAL HEREDODEGENERATION (SPIELMEYER-VOGT DISEASE)

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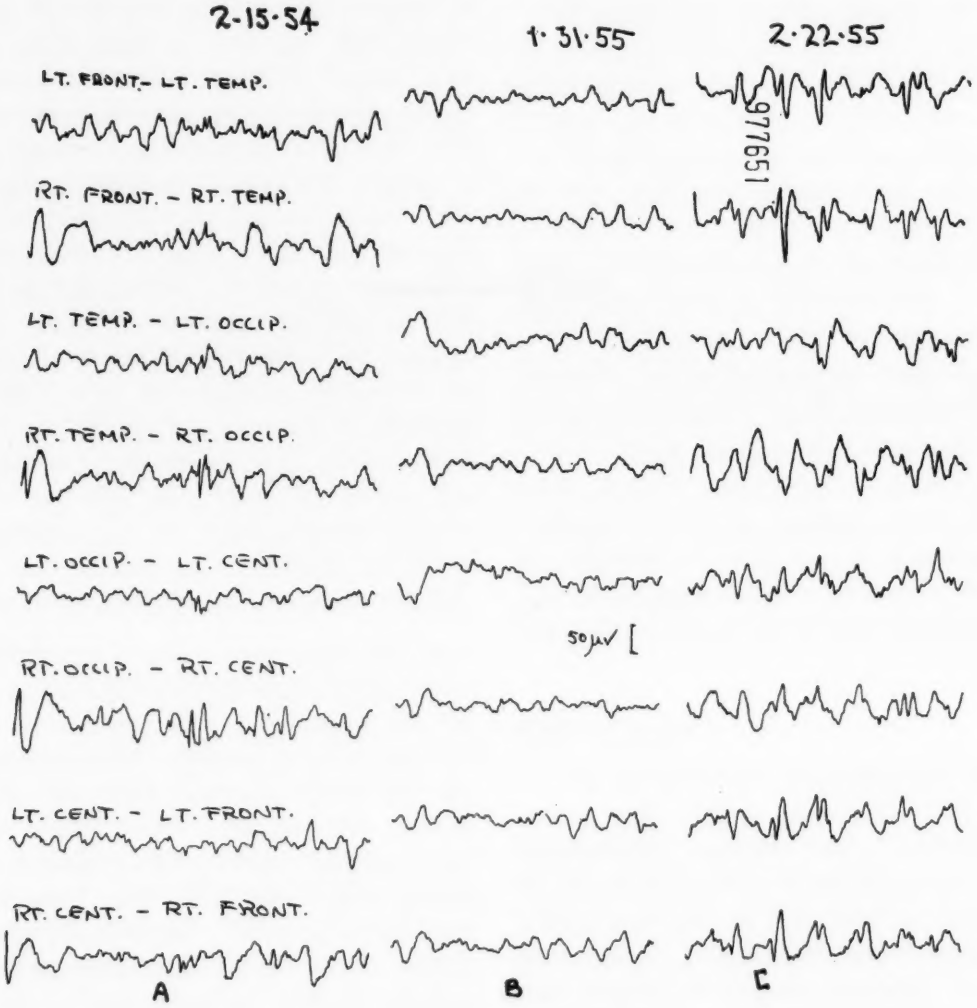
(Received for publication: June 25, 1955)

An intensive search into the available literature reveals extremely little relative to the electroencephalographic pattern in Spielmeyer-Vogt disease and nothing concerning its response to ACTH administration. It is felt, therefore, that it would prove of particular value to report the serial EEGs of two patients (sisters), their two younger siblings and parents to show not only the electroencephalographic reflection of the lipoid neuronal disturbance but also how it was affected by ACTH administration.

FIG. 1




BONNIE Z.

Spielmeyer-Vogt disease is also known as Juvenile Tay-Sachs disease, Juvenile Amaurotic Family Idiocy, or Batten-Mayou disease and is an heredofamilial degenerative disease of a Mendelian recessive type. It effects children of both sexes, of no particular ethnic group, and whose birth and early developmental history are within normal limits. About the sixth year of life there is some difficulty of vision which is associated with an initial arrest of intellectual development soon to be followed by a precipitous decline to profoundly low levels. Emotional alteration with irritability, apathy, poor attention span, and eventual complete detachment is noted. Usually grand mal convulsions are prominent observations. On clinical

examination, in addition to progressive generalized bodily deterioration more specifically one notes neuro-ophthalmological alterations. Ophthalmoscopically the early changes consist of a yellowish gray retina with slightly diminished blood vessel caliber. Within a relatively short time the peripheral regions of the retina reveal small pigmented granules whose appearance gradually progresses centrad and which resembles retinitis pigmentosa. The macular region has a brownish brick-red core with a pale halo surrounded by a peppery pigmentation. Optic atrophy is a late finding and is noted in association with fixed pupils, extra ocular muscle palsies and/or nystagmus. The initial decreased visual acuity is followed by expanding scotomata and eventual blindness. The paralysis which becomes increasingly more severe is of either the spastic or flaccid type and may be accompanied by numerous scattered fibrillations of a lower motor neuron degeneration. By the seventeenth to twentieth year the general bodily resistance is markedly decreased and the patient is easy prey for secondary infections and death.

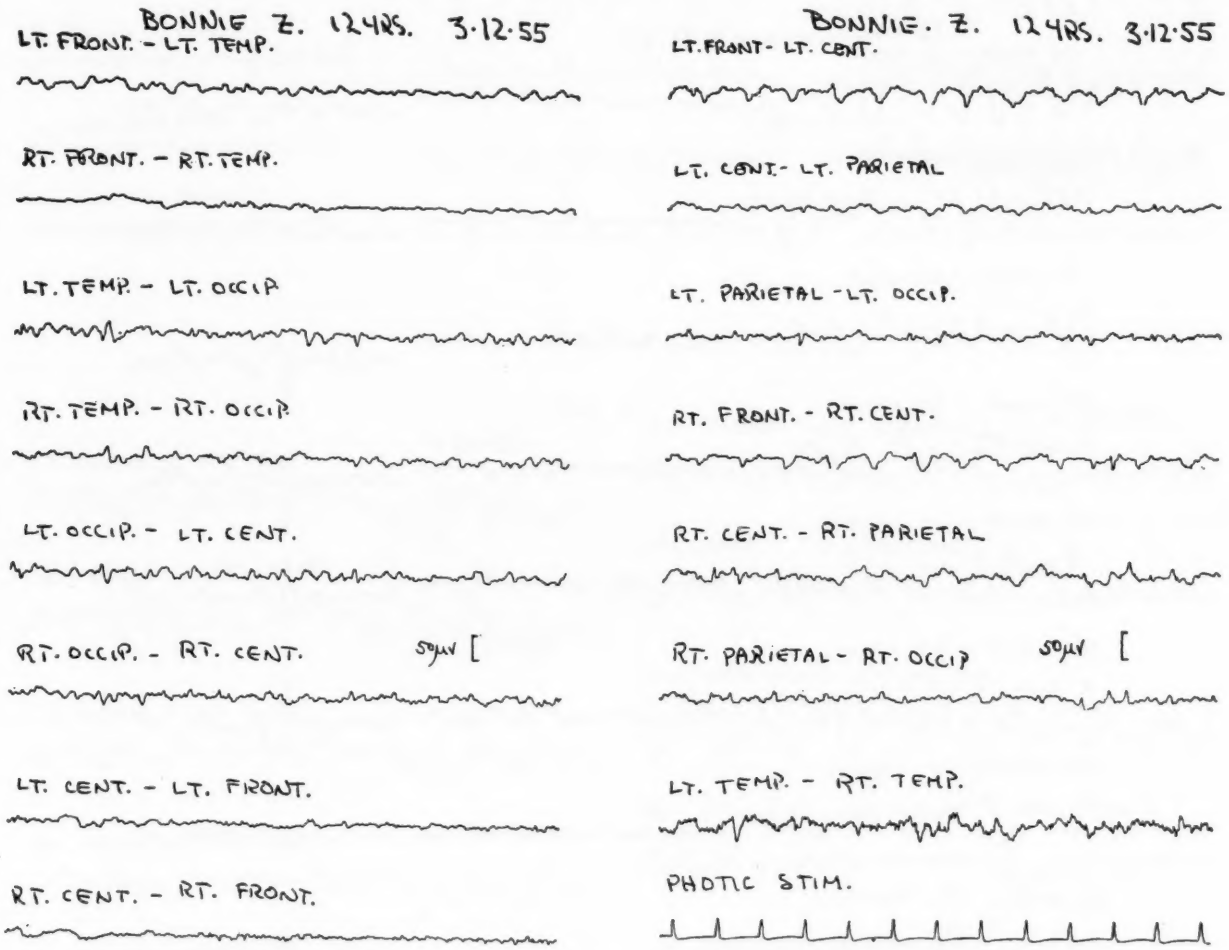

BONNIE Z. 12 HRS. 3·12·55
LT. FRONT. - LT. TEMP.
RT. FRONT. - RT. TEMP.
LT. TEMP. - LT. OCCIP.
RT. TEMP. - RT. OCCIP.
LT. OCCIP. - LT. CENT.
RT. OCCIP. - RT. CENT.
50 μV
LT. CENT. - LT. FRONT.
RT. CENT. - RT. FRONT.
BONNIE. Z. 12 HRS. 3·12·55
LT. FRONT - LT. CENT.
LT. CENT. - LT. PARIETAL
LT. PARIETAL - LT. OCCIP.
RT. FRONT. - RT. CENT.
RT. CENT. - RT. PARIETAL
RT. PARIETAL - RT. OCCIP
50 μV
LT. TEMP. - RT. TEMP.
PHOTIC STIM.

Fig. 2

*Family History* :

Both the father, Mr. Wayne Z. who was born in 1920 and the mother, Mrs. Wayne Z., three years his junior, are high school graduates and appear to be of superior intelligence. Their ancestry is mixed Scotch Irish and German stock without any Jewish members. Mrs. Z. was 19 years of age at the birth of the first child, Bonnie, and 21 at the birth of the second child, Lynn. Mrs. Z. is one of twins and in addition has three older siblings. There is no indication of neurological disease in any member of the mother's family whereas, the father's 18 year old nephew is mentally retarded and his 53 year old moderately demented paternal half aunt has had marked visual impairment with optic pallor, retinitis pigmentosa, and macular pigmentation.

Bonnie Z. weighed 7 pounds, 6 ounces at a normal spontaneous birth in July, 1942 after a nine months gestation. Her postnatal development and infancy was entirely within normal limits, such that she sat alone at 5 months, walked unassisted at 11 months, spoke her first words at 10 months, and sentences by 2 years.

Her development continued quite satisfactorily until the latter half of the sixth year when her scholastic achievement declined and social adjustment showed a withdrawl. In addition, on the third day of a relatively mild case of rubeola she had her

first of many convulsions which have gradually increased in severity and frequency and are of mixed types. Her motor coordination and capacity have fallen to a point where she is now bedfast. The I. Q. has dropped from the hight 120's premorbidly to the present 6.

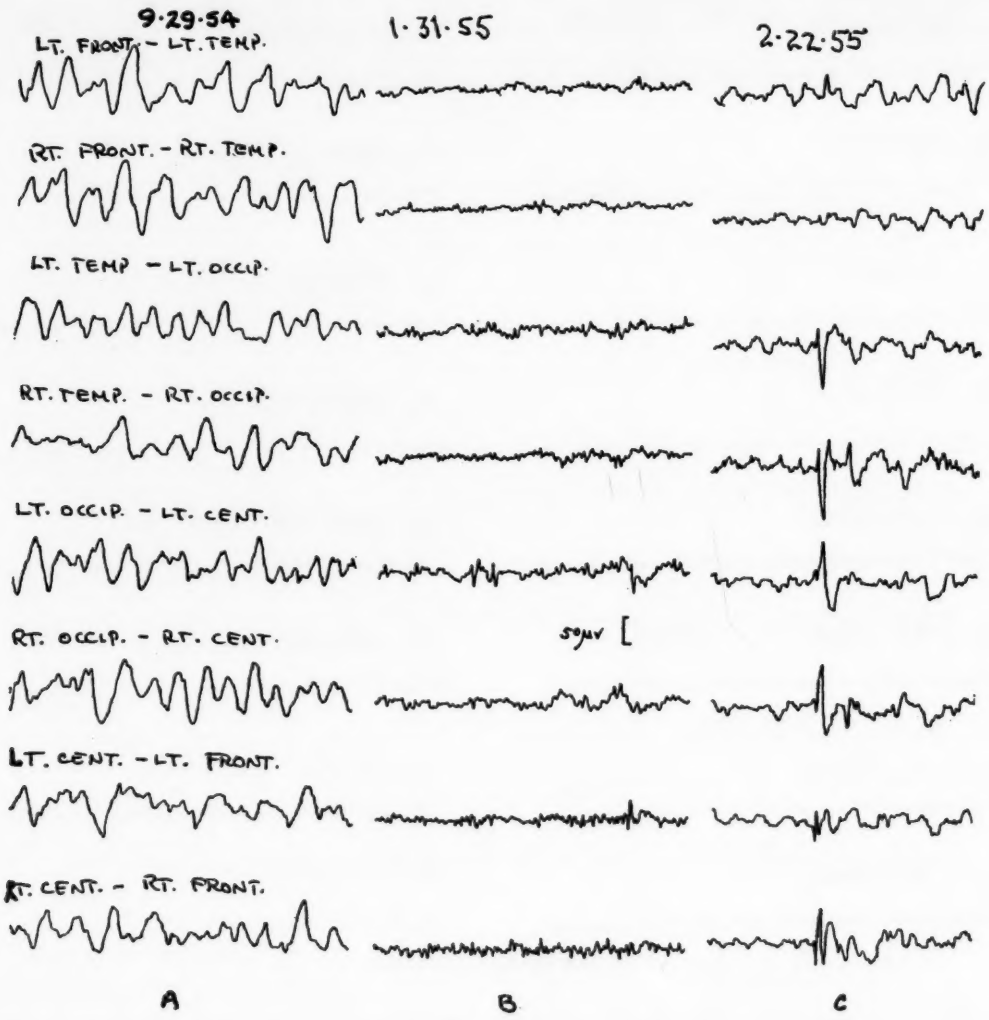
At about the age of 8½ years there began a rapid, almost cataclysmic deterioration of her entire functioning so that she began having formed visual hallucinations of a "big doggie" followed by color misperception, unpredictable unprovoked temper outbursts and subsequently apathy and echolalia, perseveration and stereotypy. The visual acuity followed a like precipitous decline from a sporadic letter elision at 8 years to phrase and line omission by 9. By 11 her vision was so impaired that she required assistance getting about. At 10½ or six months after she was able to maneuver a tricycle she became almost bedfast and incontinent of urine and saliva.

One year later, on admission to the Columbus State School, at 11½ years of age, her visual acuity was just about nil and her perception limited to shadows and movements only. Ophthalmoscopic examination revealed marked primary optic pallor, almost atrophy, vascular attenuation to threadlike size and intense retinal dark pigmentation, especially at the periphery. At the macula area there was a central brick-red brown core with a peppery pigmentation. Except for diffuse atrophy and fasiculations and a left Babinski toe sign, there were no significant abnormal neurological signs. Complete laboratory studies revealed no pathology of the endocrine, blood, osseous or visceral systems.

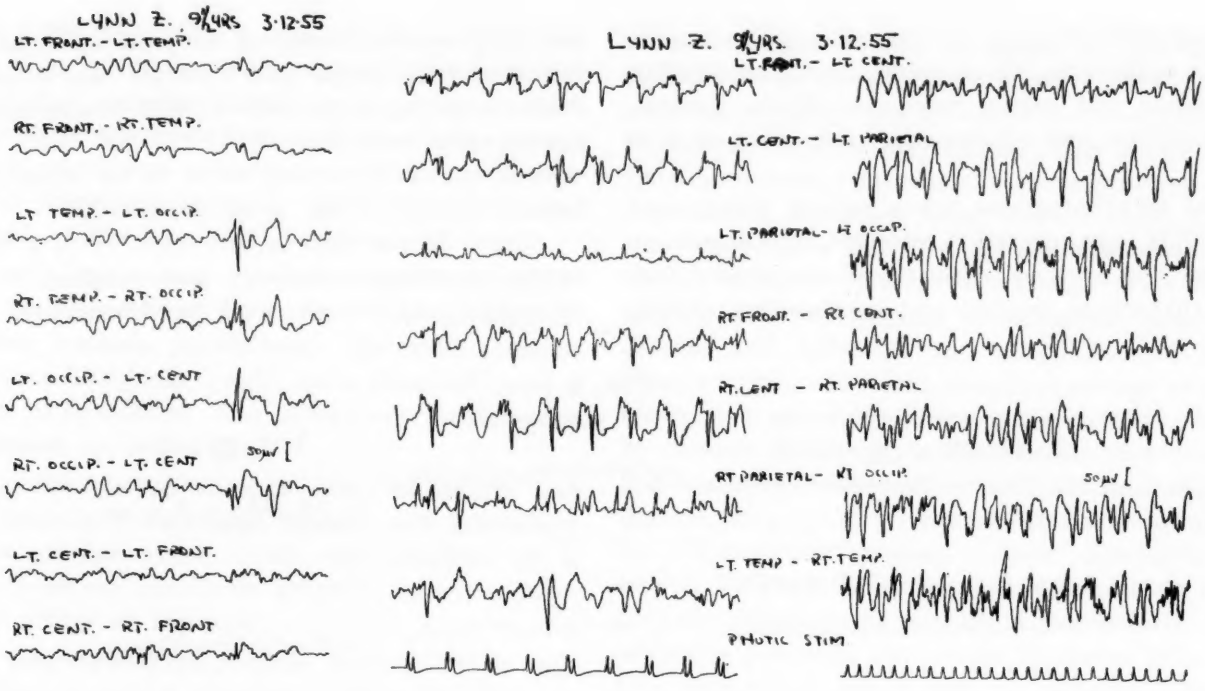
Treatment was entirely paliative since no known specific measures are known. ACTH was tried intensively but resulted in complicating hypertension, glycosuria and weight loss. Furthermore, Bonnie became very lethargic and the convulsions increased. Cessation of the use of the steroid brought about a reversal of blood pressure, urine findings, and weight. She became alert and more responsive.

*Electroencephalographic Studies*: (All the electro-

FIG. 3




LYNN Z.


LYNN Z. 9½YRS 3·12·55
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LYNN Z. 9½YRS. 3·12·55
LT. FRONT. - LT. CENT.
LT. CENT. - LT. PARIETAL
LT. PARIETAL - LT. OCCIP.
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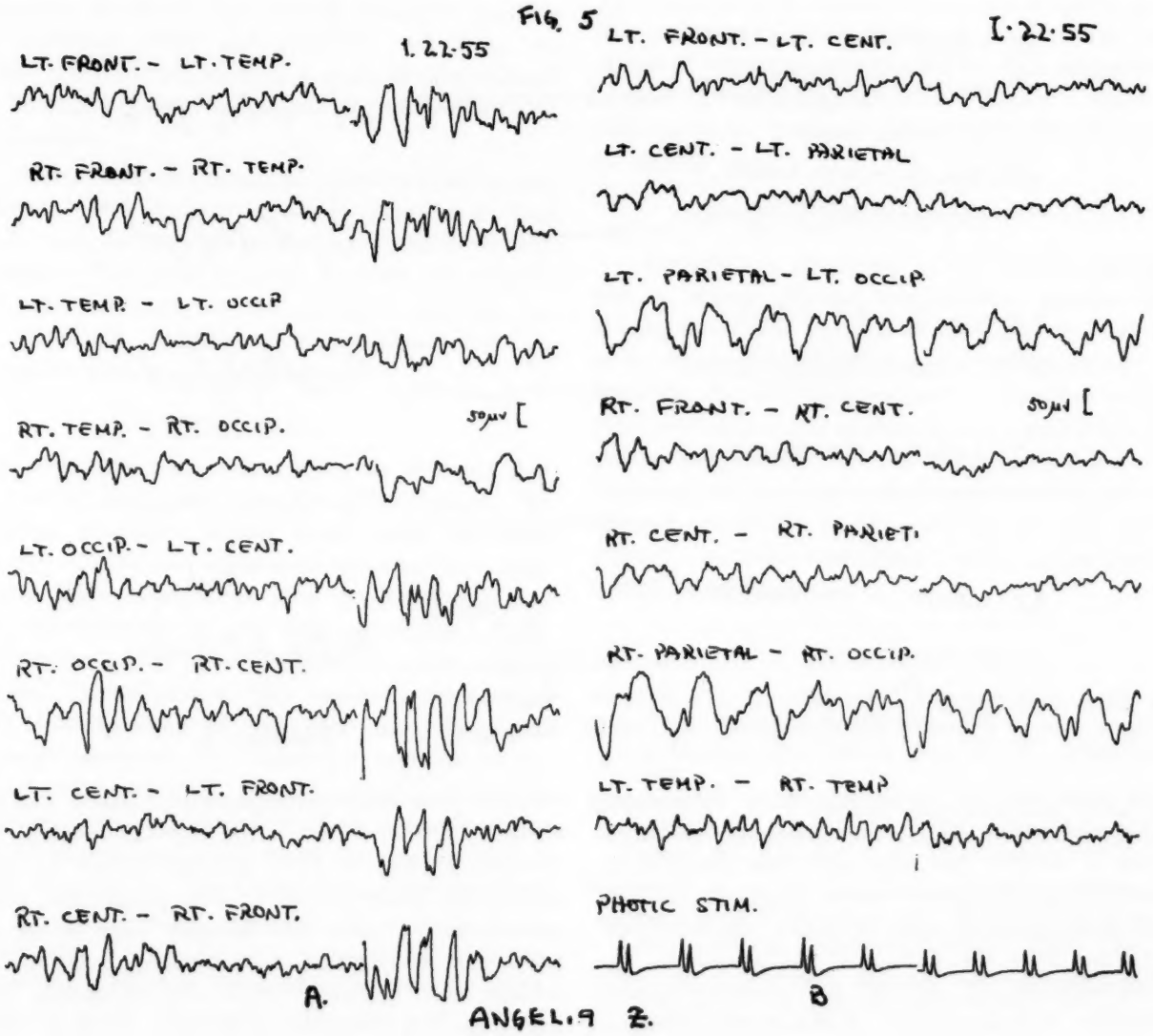
PHOTIC STIM

Fig. 4.

Fig. 5



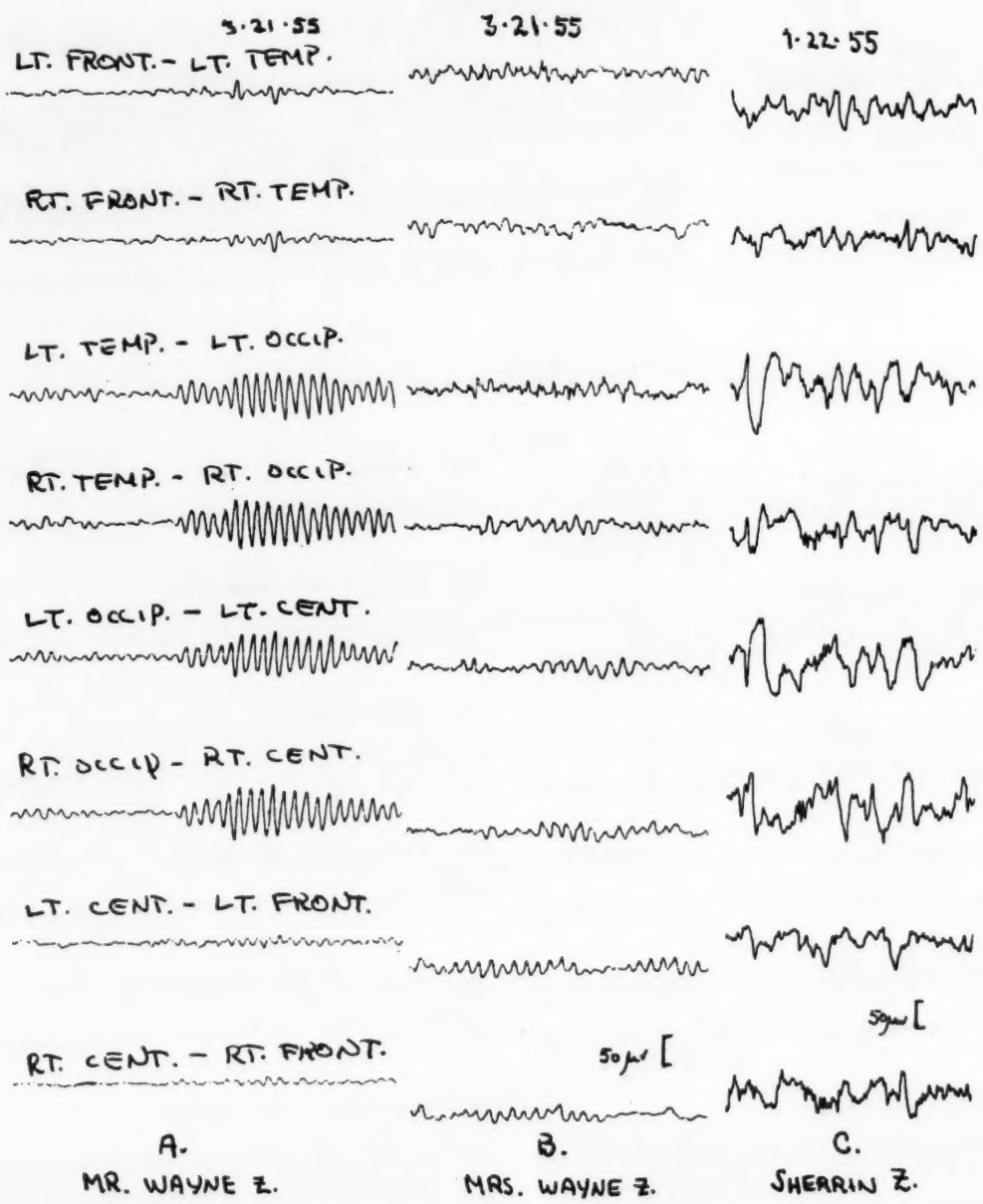

ANGELO Z.

encephalographic tracings in this series were done on Offner-D apparatus, 12 channels, using monopolar, bipolar leads and vertex reference. When feasible, hyperventilation and stroboscopic tests were used as noted.)

Serial encephalograms taken before, during and after ACTH administration revealed significant alterations. The pre-medication record manifested high voltage rhythmical slowing and synchronous spiking and with regular bursts of atypical spike and wave forms of both single and multiple monophasic and diphasic spiking in all areas of both hemispheres. One month after cessation of ACTH the EEG changes were dramatically altered so as to be considered the least abnormal of any noted previously.

Lynn, Z. was born in November 1944, a full term normal spontaneous delivery and weighing 6 pounds, 14 ounces. As far as could be determined, the im-

FIG. 6




intermixed with random spike and wave formation, more on the right than left. After one month of high daily doses of ACTH, the EEG patterns changed to a very low voltage irregular record showing less organization and disappearance of alpha and most of beta rhythms. Only the delta and theta activity remain. Continuation of ACTH for another month caused further disintegration of the EEG rhythms

mediate post-natal developmental history was entirely within normal limits. She sat unassisted at 5½ months, walked at 11½ months, talked at one year and spoke sentences at 2. She progressed along expected norms until her seventh year when her intellectual retardation necessitated withdrawl from school. Her attention span was shortened and she began having frequent petit mal seizures. One and

one half years later after a febrile gastroenteritis she had her first grand mal seizure which together with the petit mal episodes became more violent. Associated with a rapid decline of I. Q. (to a present level of 9) there was nyctalopia, echolalia, perseveration, and delusional ideation. Her motor activities diminished as did her social relationships.

As with her sister, the only significant pathological findings were of the retinae (macular pigmentation and retinitis pigmentosa), Babinski extensor toe response bilaterally (right more than left) and a cerebellar type ataxia. The laboratory studies, too, demonstrated no pathology.

Lynn was started on high doses of ACTH and showed essentially the same clinical and laboratory responses as her sister (with the addition of a moderately severe acneiform eruption over the forehead and bridge of the nose).

The electroencephalographic studies before administration of ACTH revealed a diffusely abnormal EEG with high voltage single spike activity throughout all leads. After one month of ACTH there was added much low voltage fast rhythms and one month later sporadic bursts of high voltage multiple positive spikes. However, after one month's rest from all ACTH the EEG record showed a more nearly normal pattern though with an occasional atypical spike and wave formation.

.The clinical and neurological examinations of the two patients' two younger sisters (Angela Z. and Sherrin Z.) and father and mother are entirely within normal limits. The EEG's of the parents are normal. However, the tracings of the younger siblings reveal an abnormal pattern of a non-focal type of atypical spike and wave complexes.

## DISCUSSION

Many attempts have been made to uncover distinctive biochemical alterations in this disease. To date nothing conclusive along these lines has been forthcoming. There are some authors who have suggested that this disease is due to an endocrine dyscrasia, particularly of the adrenal cortex. With recent advances by Selye and others, a new avenue of hormonal investigation was opened. Thorough laboratory investigation in the two cases discussed in this paper revealed the endocrine systems to be functioning quite normally, though administration of ACTH brought about observable clinical and encephalographical alterations which have not been reported previously. Reports of the encephalographic tracings in cases of this disease revealed non-specific convulsive patterns. This is further substantiated by the present studies, although additional interesting data is supplied by the stroboscopic activation and ACTH administration. It can be stated at this time that ACTH does, indeed, significantly alter the EEG pattern, probably due to metabolic alteration of the defectively functioning neuron. Why there seems to have been some apparent clinical improvement is undetermined. Certainly these would indicate that further observation and investigation are warranted. It is this author's opinion that though there are close clinical and pathological resemblances between this disease and Infantile Tay Sachs disease, the differences are greater and numerous enough to warrant classifying this entirely separate and apart. It might be further clarifying to disassociate this from both the confusing historical antecedents and misleading disease category by identifying it more appropriately as ''Pigmentary Retinal Lipoid Heredo-degeneration''. This would adequately and accurately indicate that the disease is an hereditary degenerative disease affecting primarily the neuron, wherever it is — cortex, cerebellum, spinal cord or ganglion. It would offer a further specific indicator, noting the involvement of the pigmentary cells of the retina and also, that this disease process results in a deposition of lipoidal material within the neuron without specifying the source or nature which, in reality, are unknown. Another objection eliminated by this suggested name is that it would drop the term ''idiocy'' which implies this to be an amentia rather than the dementia that it clearly is.

## SUMMARY

Reports are presented of two sisters, thirteen and eleven, whose clinical examination reveals the classically described picture of Spielmeyer-Vogt disease, or as the author would suggest, ''Pigmentary Retinal Lipoidal Heredodegeneration''. Detailed serial electroencephalographic studies reveal significant changes, particularly after ACTH administration. Though clinically the parents and younger sisters are entirely normal, the EEGs of the siblings are not and would strongly indicate that their further close observation would be necessary.

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# ELECTROENCEPHALOGRAPHIC CHANGES IN HYPERAMMONEMIA

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(Received for publication: December 12, 1955)

There is considerable evidence that the physiological factor, or at least one of the most important factors, in the production of encephalopathy associated with liver disease is an elevated blood ammonia. Ammonia is formed in the body in several ways: (1) in the kidney as a base saving mechanism largely through the hydralysis of glutamine; (2) in the stomach as a neutralizing agent by the action of the mucosal urease on urea; (3) as a product of cellular activity, and (4) in the gastrointestinal tract probably as a result of bacterial breakdown of urea with the amount of ammonia being proportional to the total protein intake. It is this last source of ammonia that is pertinent to our subject here. There is normally a relatively high ammonia level in the portal vein. If this substance is allowed to bypass the liver either because of a surgically performed portocaval shunt — Eck fistula — or there is production of a marked collateral circulation as a result of advanced cirrhosis, or the liver itself is too severely damaged to form urea from the ammonia brought to it by the portal circulation, there will be an abnormal elevation of the systemic blood ammonia. There is good but not complete correlation (Sherlock *et al.* 1954; Traeger *et al.* 1954) between the systemic venous blood ammonia level and the clinical signs of encephalopathy. Two reports (Adams and Foley 1953; Bickford and Butt, 1955) on the electroencephalographic findings in patients in various stages of hepatic coma have appeared. However, there is considerable lack of agreement as to the electroencephalographic pattern in this disease although one group states that the findings are typical enough to suggest a diagnosis from the electroencephalographic pattern alone and among scattered reports (Schwartz *et al.* 1954) the findings of the other group have been called ''characteristic'' although the authors of the original works state that the changes were ''nonspecific''.

This present report consists of the findings in frequent serial electroencephalograms obtained on two patients who were given oral ammonium chloride and the correlation of the wave pattern and the blood ammonia levels. Obviously our series is too small to seriously enter the argument about the general changes in electroencephalographic pattern in hepatic coma; suffice it to say that the electroencephalograms in our patients did not exhibit the rather specific types of changes noted either by Bickford and Butts or Adams and Foley.

## RESULTS

One patient, H. L., was a 23 year old male with a surgically produced portocaval shunt who had little or no liver disease; the second patient, A. P., was a 58 year old female with advanced Laennec's cirrhosis. These cases have been reported in detail elsewhere (Newman *et al.* 1955). Before the serial studies were begun, the patients were placed on a 20 g. protein diet which resulted in marked clinical and electroencephalographic improvement. Blood ammonias were obtained by a modified Conway technique.

Beginning on January 10, 1955, H. L. was given 3 g. of ammonium chloride orally each day for 4 days, then 6 g. for 2 days followed by 9 g. for one day and 7 g. for one day. The patient would cooperate only to the extent of allowing 4 electrodes to be placed on his head and hence paired frontal-posterior parietal leads were obtained. The electroencephalograms (see fig. 1), obtained on January 6, 1955, and January 10, were characterized by moderately low voltage fairly well defined 10 to 11 c/sec. alpha with rare random 6 to 7/sec. waves whose voltage did not exceed the background baseline; on the first date, two determinations of blood ammonia were 85 and 98 micrograms per 100 cc. and though no blood ammonia determination was obtained on the second date, the day afterwards two determinations revealed the blood ammonia to be 226 and 250 $\mu$g. per 100 cc. Some minimal increase in 7/sec. activity was noted on January 12, 1955, when the blood ammonia was between the 226 $\mu$g. obtained on January 10, and the 360 $\mu$g. obtained on January 13; this slowing was much more evident on January 14, at which time there was also definite disruption of the regular alpha rhythm. The blood ammonia level on January 14, was 326 $\mu$g. per 100 cc. On January 17, but little alpha was found in the electroencephalogram and the record was characterized mainly by 3 to 6/sec. activity whose amplitude was slightly greater than noted in the previous record; the blood ammonia level had increased to 3290 $\mu$g. per 100 cc. The electroencephalogram on January 19, 1955, coincided with a blood ammonia level of 332 $\mu$g. per 100 cc. and the record resembled the one obtained

on January 12, and by January 21, the record returned to its previous baseline determination, 85 μg. per 100 cc. No paroxysmal bursts or triphasic waves were seen. Slow wave activity appeared synchronously on both sides. It was apparent that the first definite electroencephalographic change was noted when the blood ammonia level was 326 μg. per 100 cc.

In the case of A. P., she was begun on ammonium chloride on December 7, 1954. She was started on 1 g. orally each day until December 12, when it was increased to 1.5 g. for two days and then on December 14, she was given 2 g. Bipolar 14 electrode placement electroencephalograms were obtained (see fig. 2). Electroencephalogram on December 6, 1954, was characterized posteriorly by 7 c/sec. waves of moderate to moderately low voltage with a small amount of 6/sec. activity; on the following day her blood ammonia level was 79 μg. per 100 cc. On December 9, the posterior 7/sec. activity was significantly decreased only to be replaced by an increased amount of 5 to 6/sec. activity both posteriorly and anteriorly; this corresponded to a blood ammonia level of 240 μg. per 100 cc. The following day the electroencephalogram was characterized by generalized 3 to 5/sec.

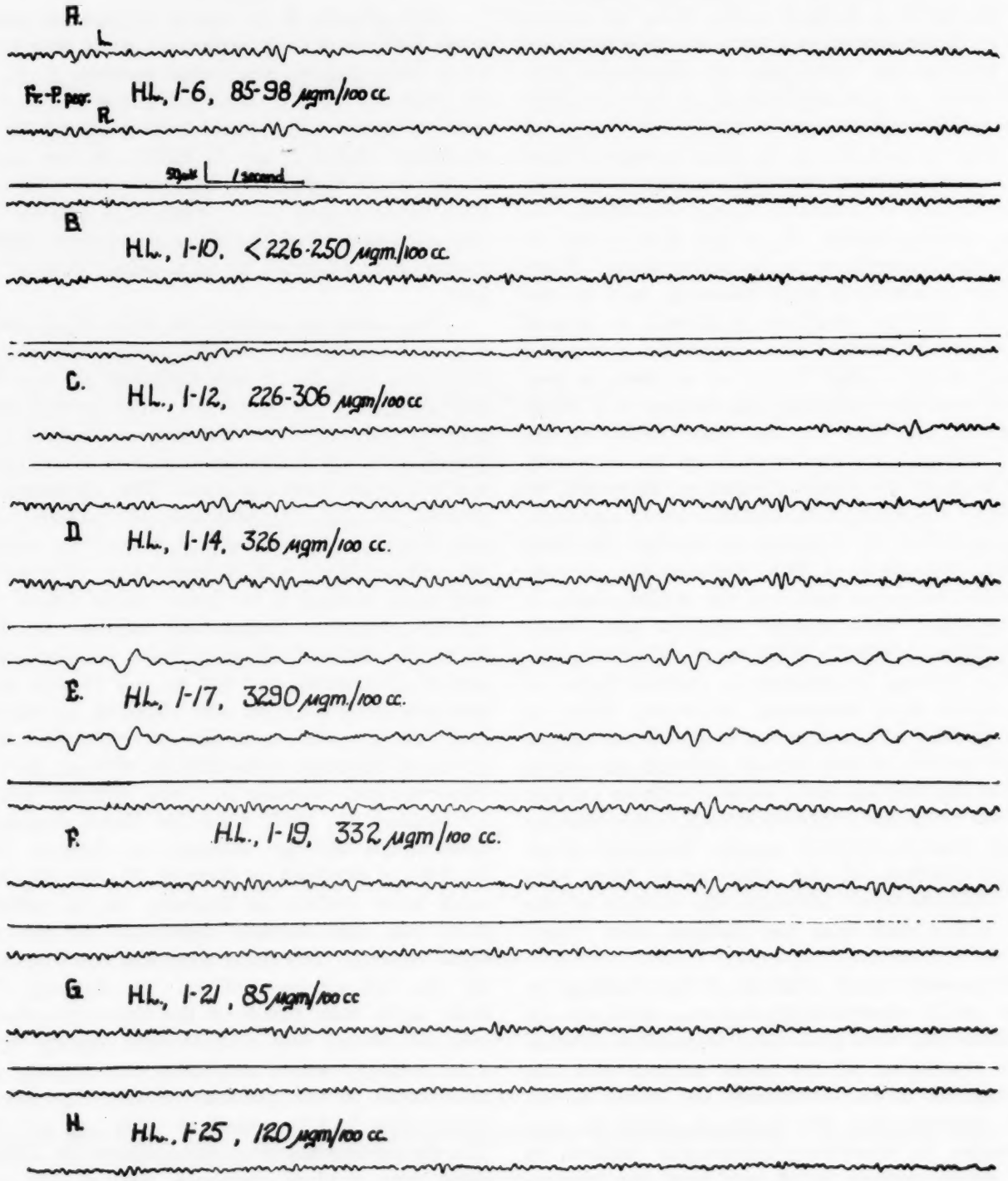


**Fig. 1**

Samples of serial electroencephalograms with the corresponding blood ammonia level in a patient (H. L.) with a portocaval shunt who had little or no liver disease.

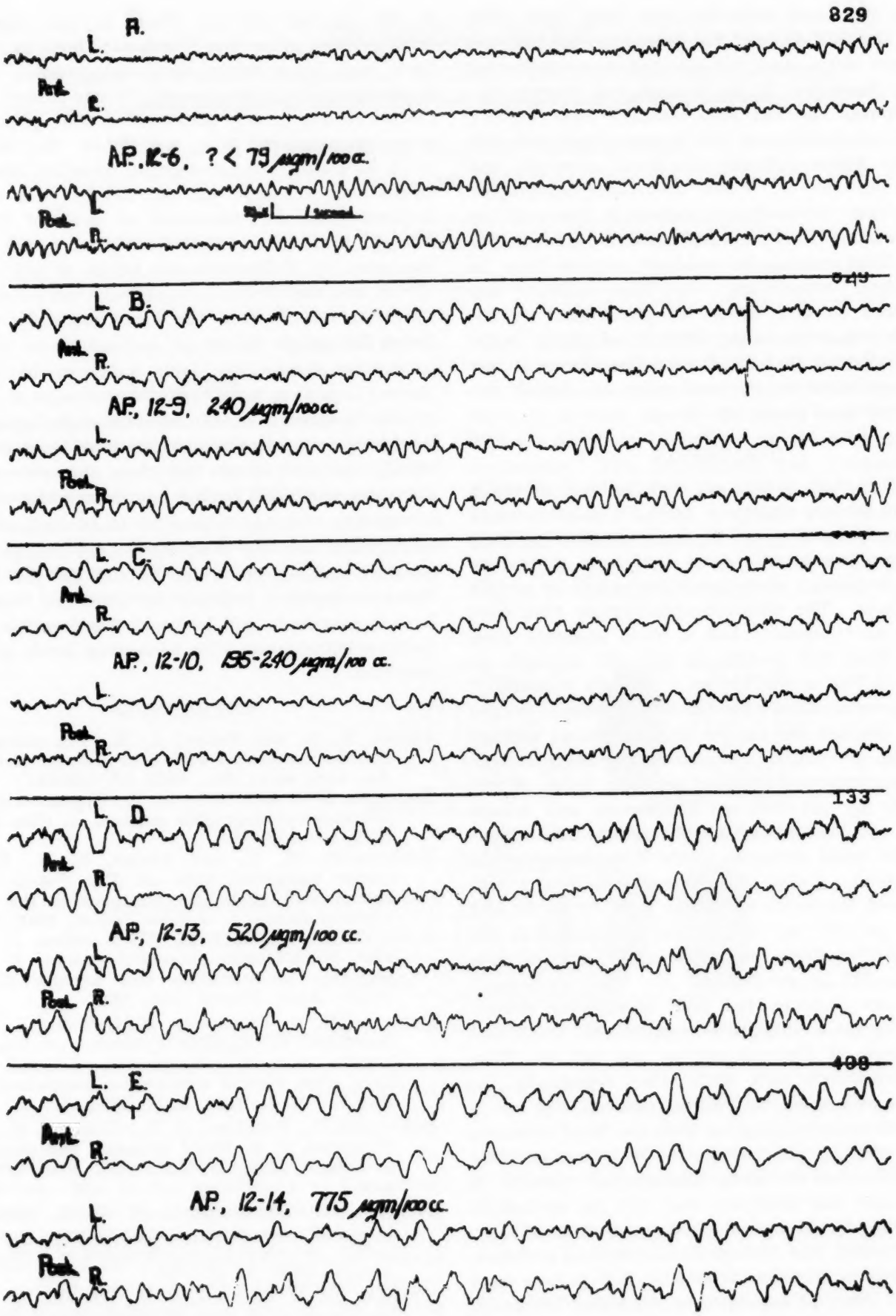


Fig. 2

Samples of serial electroencephalograms with corresponding blood ammonia level in a patient (A. P.) with advanced Laennec's cirrhosis.

activity; the blood ammonia level must have been between the 240 obtained the preceding day and the 195 μg. per 100 cc. that was obtained on the following day. By December 13, the patient had become confused whereas she had been mentally clear before; her electroencephalogram had become slower and with a slightly higher voltage; the blood ammonia was 520 μg. per 100 cc. These electroencephalographic abnormalities increased the following day and her blood ammonia level had increased to 775 μg. per 100 cc. That evening she suddenly expired from an intracerebral hemorrhage. The slow activity was synchronous on both sides; no paroxysmal or triphasic waves were seen. Review of these serial records indicated that the first major change in her electroencephalogram occurred when the blood ammonia level was 240 μg. per 100 cc.

## DISCUSSION

Phillips *et al.* (1952), charted the blood ammonia levels and made a statement as to the appearance of the electroencephalogram in a group of 4 patients with impending hepatic coma that were given ammonium containing ion-exchange resins and/or protein and/or urea. The electroencephalograms that were reported as ''normal'' had a blood ammonia level ranging from 210 to 430 μg. per 100 cc. with an average of 360 μg. per 100 cc. ''Slightly abnormal'' records were obtained when the blood ammonia ranged between 230 and 440 μg. per 100 cc. with an average of 344 μg. per 100 cc.; two abnormal electroencephalograms correspond to blood ammonia levels of 320 and 1500 μg. per 100 cc. McDermott and Adams (1954), obtained electroencephalograms and determined the blood ammonia levels three times in the same patient. Twice the electroencephalogram was normal and the blood ammonias were 50 to 60 and 125 μg. per 100 cc. On the one occasion that the electroencephalogram was abnormal the blood ammonia was 325 μg. per 100 cc.

In our patients, the first significant electroencephalographic changes correspond to blood ammonia levels of 326 and 240 μg. per 100 cc. This, then, corresponds well with other reports in the literature except one of Phillips patients who had a normal electroencephalogram with the blood ammonia level of 430 μg. per 100 cc. If it is recalled that the criteria for electroencephalographic changes is quite inexact and arbitrary and that the method of determining blood ammonia is fraught with considerable difficulty, this correspondence between our findings and several others in the literature is even more striking. It would appear, then, that the ''critical'' blood ammonia level at which there is the first major electroencephalographic change is about 200 to 400 μg. per 100 cc. There is, too, suggestive evidence that after this ''critical'' level is reached there may be a fairly rapid deterioration of the electroencephalographic record. In our patient, A. P., the record was grossly abnormal at 530 μg. and only somewhat worse at 775 μg. per 100 cc. The character of H. L.'s electroencephalogram, when his blood ammonia level was 3290 μg. per 100 cc., was not too different than A. P.'s record at levels of 520 and 775 μg. per 100 cc. A definitely abnormal record was noted by McDermott and Adams at 325 μg. per 100 cc. and one of Phillip's patients had a definitely abnormal record when the blood ammonia was as low as 320 μg. per 100 cc.

## SUMMARY

1. Correlation of the electroencephalogram and the blood ammonia levels which have been obtained serially in two patients has been observed and the literature pertinent to this has been reviewed.

2. The ''critical'' level of blood ammonia that corresponds with the first significant change in the electroencephalogram is 200 to 400 μg. per 100 cc. There is suggestive evidence that after this ''critical'' level is past there will be rapid deterioration of the electroencephalogram with increasing levels of blood ammonia.

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# *TECHNICAL NOTES*

Editor for Western Hemisphere and Far East, J. KNOTT, Iowa City, Iowa, U.S.A.
Editor for Europe and Middle East, H. SHIPTON, Bristol, England

## A STRAIN-GAGE PNEUMOTACHOGRAPH

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(Received for publication: February 21, 1956)

This communication reports an apparatus that is capable of recording tidal and minute respiratory volume in experimental animals for prolonged periods. It consists of a screened-chamber tracheal cannula pneumatically connected to a strain-gage manometer, which produces a modulated signal that is amplified and recorded by a Grass clinical EEG inkwriter.

The tracheal cannula (fig. 1) was constructed according to the principles developed by Silverman and Whittenberger (1950a, b) and Lilly (1950). In studies on humans, they employed a close-fitting face mask equipped with an orifice covered with a fine wire screen. Due to the impediment of the screen, inspiratory inflow and expiratory outflow set up inside the mask pressure differentials being linearly proportional to the flow rate. The outer opening of the cannula employed here was similarly covered with 400 line/inch Monel wire screen. The interior of the chamber was provided with a manifold to equalize the pressure and to prevent spurious effects due to the flow of air across the orifice of the stem. A ring made of bakelite was used to assemble the manifold and screen within the cannula.

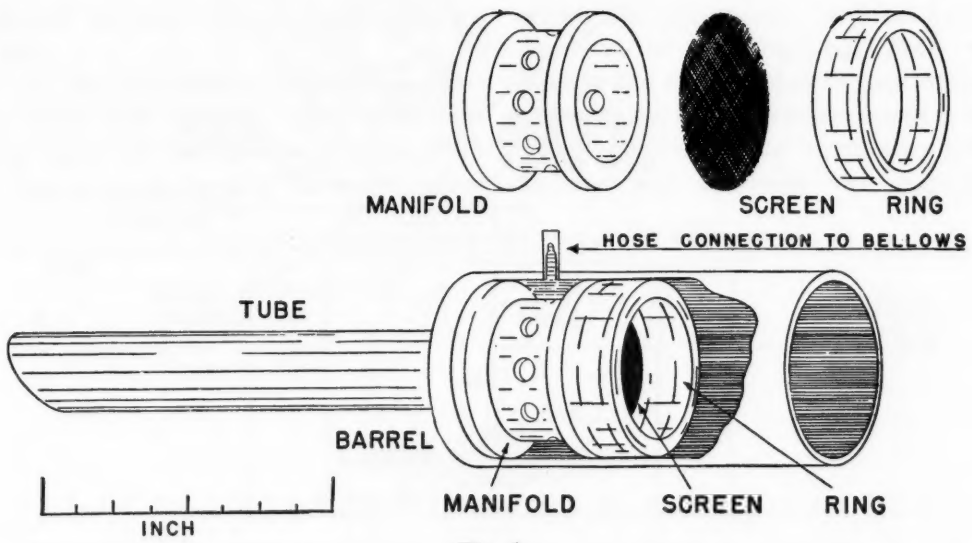


**Fig. 1**
Screened-chamber tracheal cannula.

Pressure measurements showed that the impediment of airflow due to the screen was 0.1 mm. of $H_2O$ per liter/min. of airflow, as measured on a water manometer. This impediment was considered negligible or, at most, equivalent to no more than a trace of mucus in the trachea. The pressure differential remained linear, negative with respect to barometric pressure on inflow and positive with respect to barometric pressure on outflow, up to 100 liters/min. No instantaneous airflow rates exceeding 80 liters/min. have been observed in our studies in cats.

The electro-mechanical transducer was constructed as shown in figure 2. Three feet of 1 mm. i.d. rubber hose was used to connect the cannula to the bellows. Since the pressures involved were slight, even soft rubber tubing was sufficiently resistant to expansion for this use.

The bellows were made of thin, hard-drawn

beryllium-copper wafers with expanding concentric pleats, a type used in aircraft rate-of-climb instruments. The bellows came with a long, spirally-wound bleeder line open distally; a stem suitable for coupling was inserted between the bellows and the end of the beam. Four type SR4 paper-wire strain gages (Baldwin Locomotive Co., Swarthmore, Pa.) were attached with Duco acetate cement, according to

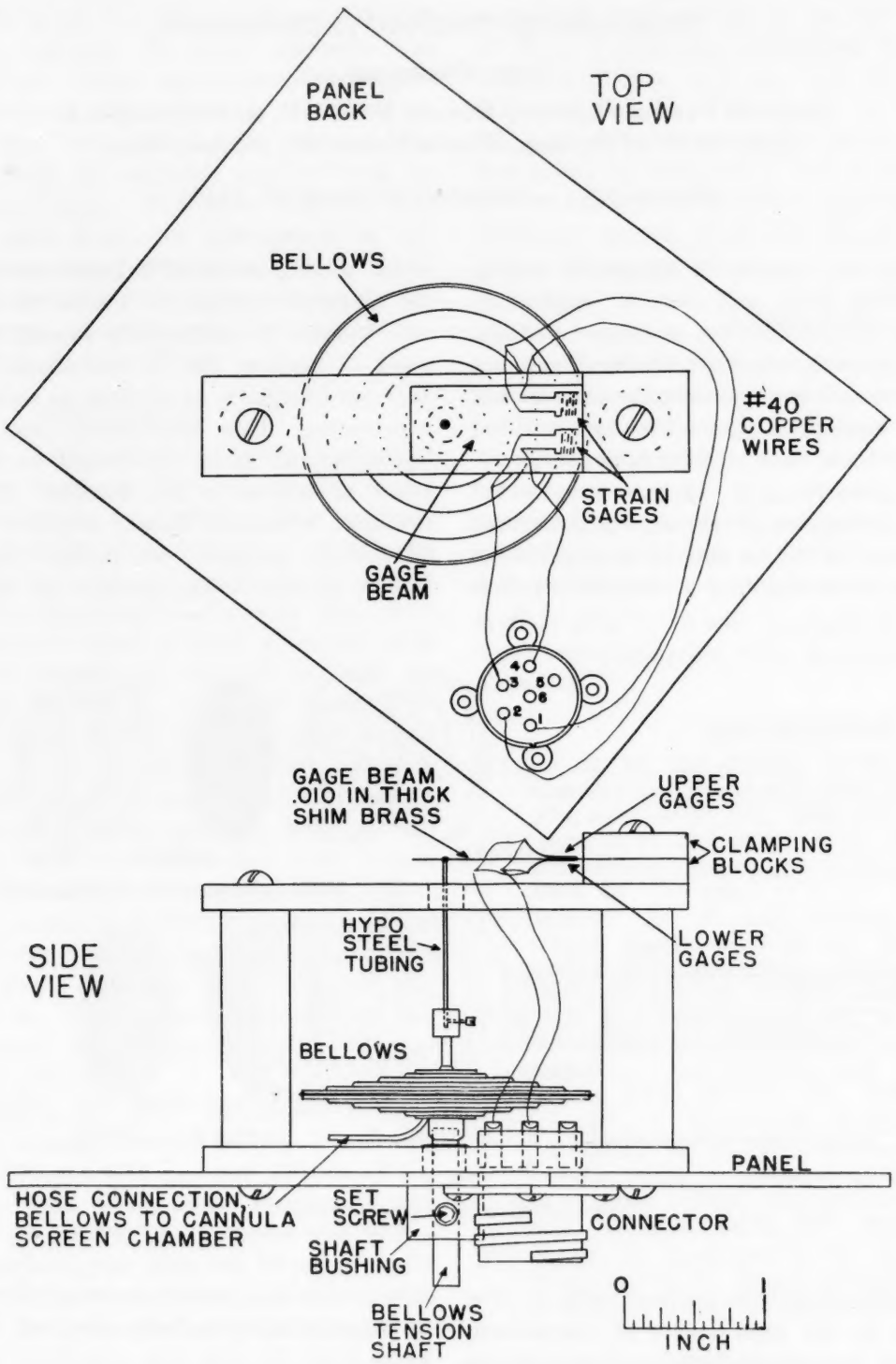


Fig. 2

Top and side views of wafer bellows, cantilever and attached strain gages, and electro-mechanical transducer.

the hose-connection from the cannula was substituted.

A cantilever beam of shim brass was placed in line with the working axis of the bellows, and a mechanical connection of hypodermic steel tubing directions provided by the manufacturer, to the beam at its root, two gages on each surface of the beam. These were connected to comprise a balanced ring-type modulator. Only gages of the same manu-

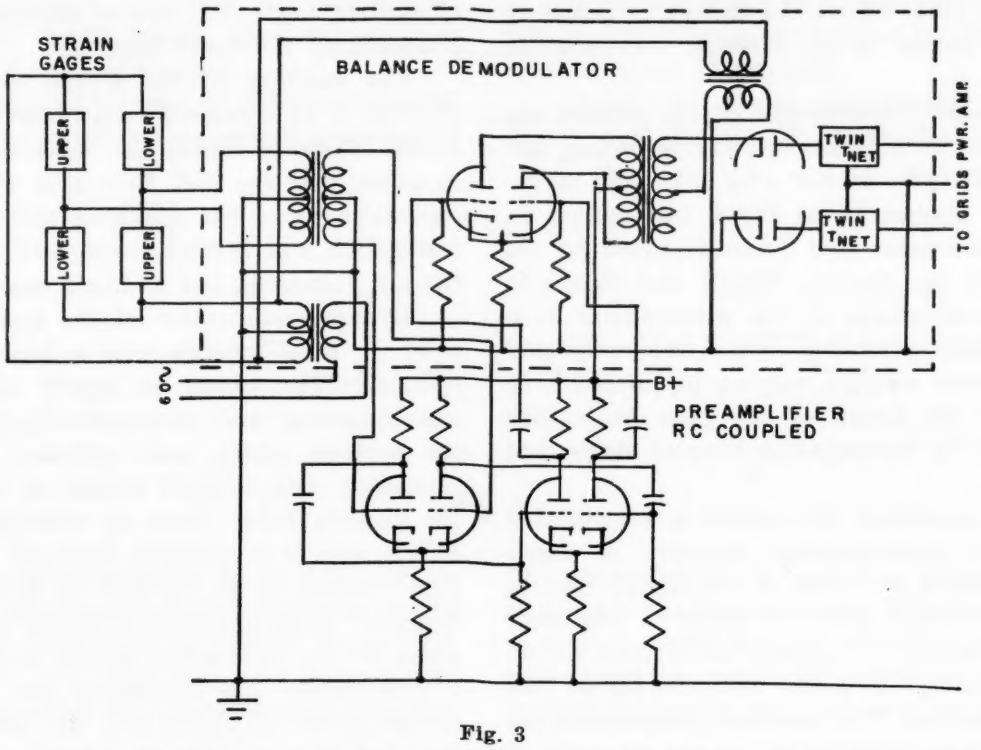


Fig. 3

Generalized electrical scheme of strain-gage bridge, 60-cycle carrier source and modulated carrier input, capacity-coupled preamplifier, demodulator and filter, and direct coupling to inkwriter power amplifier grids.

facture batch should be used for a component assembly such as this.

Adjustment of the transducer requires a prestressing of the beam and bellows. This is accomplished by pulling down on the bellows tension shaft until the gage beam is noticeably stressed, after which the adjustment is fixed by means of the setscrew in the shaft bushing. Thus, when positive pressure in the cannula due to expiratory outflow expands the bellows, the gage-beam stress is relieved, while negative pressure due to inspiratory inflow contracts the bellows and increases the gage-beam stress. The

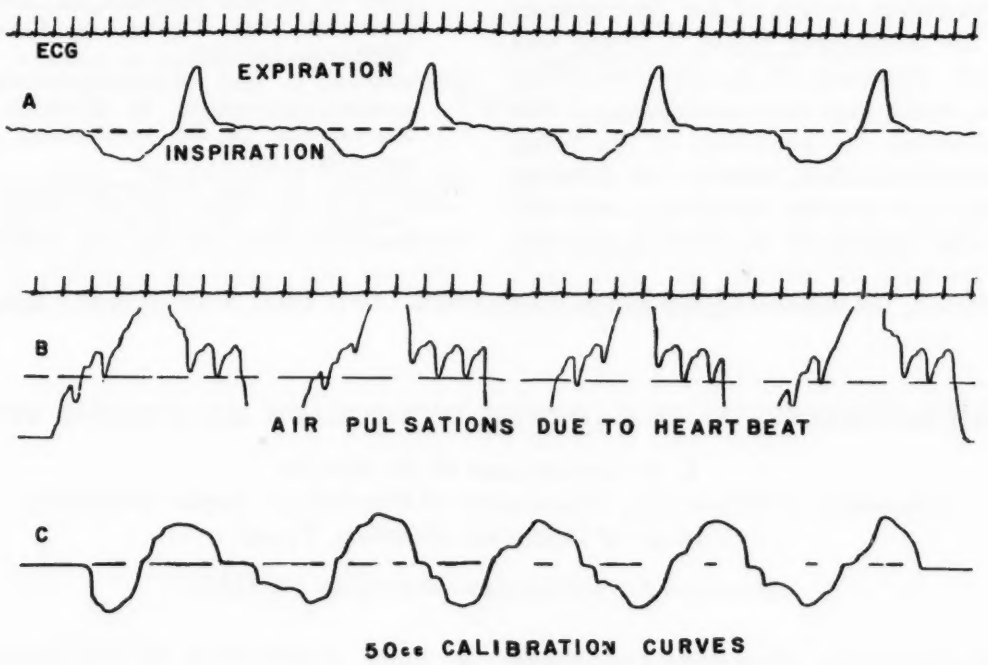


Fig. 4

A, records of respiratory periods with simultaneous ECG. B, respiratory periods with amplification 50 times that in previous record. C, Calibration curves made by drawing 50 cc. air volumes to and fro through cannula with a syringe.

prestress on the beam allows the change in phase of the respiratory period to go through zero without slackness.

The mechanical displacements of the bellows are transduced by the strain gages into corresponding modulations of a 60-cycle carrier (fig. 3). The modulated carrier is applied to an input transformer in the balance demodulator unit (manufactured by the Grass Instrument Co., Quincy, Mass.) and thence to the push-pull input stages of the preamplifier of a Grass clinical EEG inkwriter. Since the modulated carrier is a 60-cycle voltage, varying in amplitude in accordance with the action of the gage beam, this voltage is passed by the capacitor-coupled stages and amplified.

Sufficiently amplified, the carrier is demodulated by diodes in a phase-sensitive detector or demodulator. To preserve the sense of the signal, that is, to give output voltages that are equal in amplitude for a given imbalance in opposite directions, an in-phase 60-cycle voltage is mixed with the signal just prior to demodulation. The combined components are removed after demodulation by means of twin T networks, leaving a signal envelope proportional to transducer displacement. From demodulation through carrier filtering, direct coupling is maintained up to the pen writer. This preserves the response of the apparatus down to zero frequency.

The sensitivity and stability of the strain-gage pneumotachograph are evident in figure 4. Figure 4A shows the inspiratory periods accompanied by the electrocardiogram (ECG) of the cat. During the passive period and during periods of low flow rate, as during most of the inspiratory phase, a ripple was noted in the record. Pinching off the tube connecting the cannula to the strain-gage manometer stopped this ripple, thus eliminating the possibility of its being some sort of electrical artifact. Finally, by listening with a stethoscope and also by comparing with the ECG record, it was established that the ripple was of cardiac origin, i.e., due to the slight air movement produced by the heart beat.

The stability of the system allowed the amplification to be increased by a factor of 50, giving the record shown in figure 4B. Here the sensitivity was so great that the full flow rate of inspiration and expiration drove the amplifier system to cutoff, but restoration was instantaneous, without blocking, and the air pulsations due to heart beat were prominent.

Dynamic calibration of the system is made with a 50 cc. glass syringe with a lap-fitted piston and cylinder. The piston is lightly oiled to insure a smooth-sliding and pneumatically-tight fit between the syringe piston and cylinder. The syringe is connected with a short length of rubber tubing to the cannula tube. Thus, by withdrawing the piston 50 cc. and then pushing forward it is possible to pass volumes of air to and fro through the cannula chamber. Such a record is shown in figure 4C. The areas of the calibration curves are determined with a planimeter. By measuring the areas under the curves shown in figure 4A, the volume per inspiration and thus the minute volume can be determined.

This apparatus has also been used successfully to record human respiratory volume by substituting a mask for the cannula.

The system described does the work of a direct-coupled amplifier without encountering the drift and instability inherent in such amplifiers.

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# AN IMPROVEMENT TO THE OFFNER DYNOGRAPH RECORDING SYSTEM

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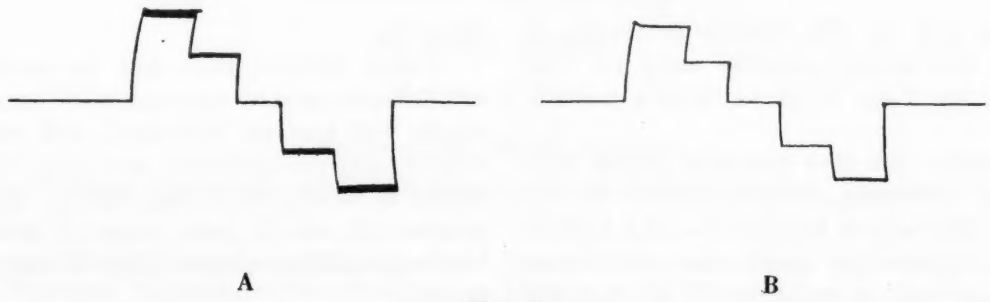
(Received for publication: November 10, 1955)

Under certain conditions, when using the Offner dynograph there is the development of vibrator hash in the record as the pen departs from the mid position. In the experience of this laboratory this phenomenon can be either eliminated or minimized by a minor modification in the dynograph amplifier output circuit. This modification consists of inserting a 5 ohm balancing potentiometer in the output circuit. When this component has been inserted in the circuit, we have noted a consistent reduction in

hash and a substantial reduction in interchannel interference, when large inputs are used on one channel and small inputs on another.

The chief source of the hash is either unbalanced vibrator duty cycles or unbalanced output transformer windings or both. The inclusion of a manually set balancing control compensates largely for these effects as can be seen by comparison of figures 1A and 1B. In figure 1A, the recording system was connected to an input signal which was varied from a negative value to a positive value. No balancing control was present in the output. On the other hand in figure 1B, the same signal was applied with the balance control adjusted to minimize the hash. The improvement in operation is obvious.

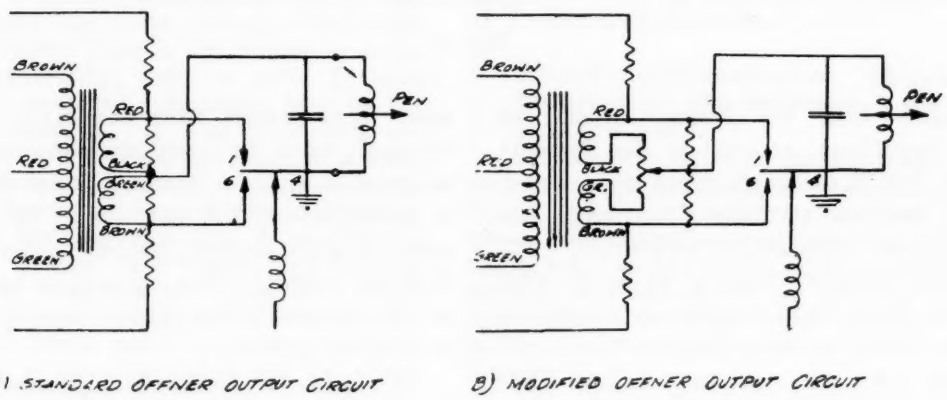


A B

Fig. 1

There is a minor loss of overall sensitivity, when this change is made in the circuit. The loss is in the order of about 15 per cent.

Figure 2A shows the general Offner output circuit, and figure 2B shows the modified circuit. The potentiometer is used as a balancing center tap to balance the push-pull pen deflecting voltage which is resynthesized by the vibrator. In practice, the adjustment is made by applying a signal which deflects the pen to near full amplitude. The potentiometer is then rotated until the hash is reduced to a minimum. Once the adjustment is made, it is fairly constant throughout the useful life of the vibrator. Only when the vibrator is replaced it is necessary to readjust the potentiometer.




A) STANDARD OFFNER OUTPUT CIRCUIT B) MODIFIED OFFNER OUTPUT CIRCUIT

Fig. 2

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*Reference*: GEDDES, L. A. and MILLAR, H. D. An improvement to the Offner dynograph recording system. *EEG Clin. Neurophysiol.*, **1956**, *8*: 520-521.

## REPLY TO MR. GEDDES

F. F. Offner, Ph.D.

(Received for publication: March 12, 1956)

The preceding note by Mr. Geddes is useful, if only in pointing out several possible ways to "go wrong" in using the Type D series EEG's for d-c recording.

Mr. Geddes points out that base-line ripple only appears with d-c recording. There should be no real difference in this respect between d-c and normal a-c use. Thus, it appears his results may be due to the type of input circuit he employs. It is essential that the circuit be rather carefully designed — as is true with most sensitive electronic devices. Few engineers are familiar with the design details of chopper-converter amplifiers, as used in the Type D. We have therefore felt it desirable to provide standardized d-c input couplers (Offner Electronics Inc. Type 9138), to insure satisfactory operation. The type of performance obtained from a Type D3 with d-c input, using the Type 9138 coupler, is illustrated in figure 1. This shows a recording of d-c input signal of only 300 μV. the relative freedom from base-line ripple, in spite of the very high gain, is apparent. Mr. Geddes has not used this coupler in his work.

Other factors must also be considered. If the rated input source impedance is exceeded, base-line ripple will also be increased, and, of course, a defective chopper-converter can give a ripple considerably in excess of normal limits. Mr. Geddes' suggestion can aid in some cases of defective choppers, but replacement of the plug-in unit would be preferable.

It is not believed that the suggested change will actually have any effect on cross-talk between channels. This results from capacitive coupling between channels when an input some thousand or more times as great is applied to one channel as to another. This is possible without over-load, by reducing the respective gain control, but the coupling can occur before the control. The obvious is to attenuate signals to a reasonable amplitude before their application to the amplifier.

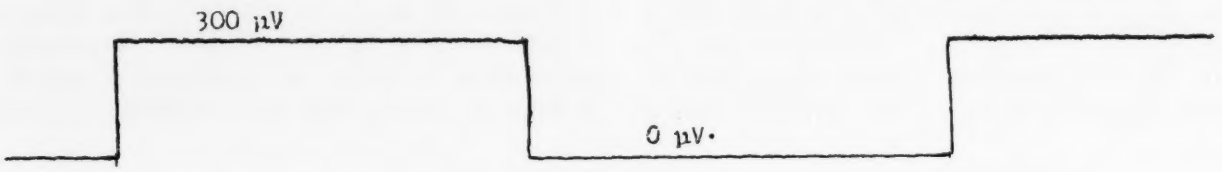


Fig. 1

We wish to thank Mr. Geddes for allowing us to review his manuscript before publication, and the *Journal* for the opportunity to reply.

# SOCIETY PROCEEDINGS

## THE EASTERN ASSOCIATION OF ELECTROENCEPHALOGRAPHERS

### Laurentian Ski Meeting

St. Adele, Quebec

March 1-4, 1956

*Secretary*: Dr. JOHN SCOTT

Toronto General Hospital, 136, Sheraton Avenue, Toronto, Ont., Canada

**1. Effect of "tranquilizing" drugs on EEG. — W. T. LIBERSON, Veterans Administration Hospital, Northampton, Mass.**

The present study is a part of an investigation aiming at an evaluation of the price the patient may have to pay in terms of abnormal functional psycho-physiological changes in order to be tranquilized by very high doses of drugs recently introduced in psychiatry. Under the influence of a prolonged reserpine therapy (average dose 7 mg. daily), some patients do not show any change of the brain wave spectrum. However, when the change occurs, it consists of a shift toward the theta range, often more pronounced in the anterior than in the posterior areas of the brain. Exceptionally, such a shift is only transitory, a partial recovery occurring despite the continuation of the therapy. It was previously reported (Rinaldi and Himwich) on the basis of animal experimentation that the effects of reserpine on the brain stem reticular formation are not of a depressing nature. The present investigation failed however to detect any increase in the fast component of the brain wave spectrum. Patients on combined chlorpromazine and reserpine therapy, exhibiting a significant shift in the brain wave spectrum, show a progressive return to a pre-drug spectrum in about three weeks after the complete suspension of therapy. It is possible that in the future, the EEG control of the medication will help in the establishing of an optimal dose of the tranquilizing drugs for individual patients without shifting the brain wave spectrum below the normal values.

**2. A measurable neurophysiological factor of psychiatric significance. — CHARLES SHAGASS, Allan Memorial Institute of Psychiatry, McGill University, Montreal.**

The sedation threshold is determined by measuring the EEG fast wave response produced by intravenous sodium amytal. This test was originally developed as an objective method of measuring tension or anxiety; it also seems to measure several other important psychiatric variables. For example, the threshold differentiates between neurotic and psychotic depressions and is correlated with the relative predominance of hysterical or obsessional personality traits.

The purpose of this study was to determine whether the sedation threshold data could be used to define differences in neurophysiological function between different types of psychiatric patients. Sedation threshold curves (frontal fast wave amplitude as a function of amount of amytal) of 400 patients and 45 control subjects were analyzed statistically. Although there was great individual variation in amplitude at the threshold point, the means of different diagnostic groups were almost identical. This indicated that the threshold measures the *rate* of brain response to barbiturates, a function which may be interpreted in terms of concepts of excitability. Rate differences could be expressed in simple mathemetical form, since the sedation threshold curve became rectilinear when the logarithm of the amplitude variable was used in plotting.

The results seem to support certain theories of brain function in psychiatric disorder, such as those of Pavlov and Eysenck.

**3. Electroencephalographic observations during intracranial electrotherapy. — JUAN NEGRÍN, Jr., New York.**

An electric current administered directly to the brain through intracranial electrodes to treat mental illness and other conditions has been in use for some time. This technique was based on the hypothesis that an electric current might be more effective if received directly and selectively by specific brain areas than if it reached the brain in an assumed diffuse manner as in the standard methods of "external electrotherapy".

The improvement of mental symptoms and syndromes with this procedure, when external electrotherapy failed, was strong enough evidence in favor of that hypothesis. However, it was always felt that it would be desirable to test the validity of the empirical principles on which this technique was based with more objective findings. Such an opportunity presented itself when a group of deteriorated psychotics were treated with a combination of psychosurgery and electrotherapy.

After a limited frontal leucotomy, intracranial electrodes were placed subpially in direct contact with the surface of the cortex above the undercut frontal lobe. Other electrodes were placed on both hemispheres and left in position after closure of the scalp. The intracranial electrodes were made of very fine tantalum wire properly insulated. At different postoperative periods of time electroencephalograms were taken with the usual scalp surface electrodes in combination with the intracranial electrodes. The standard methods of non-convulsive external electrotherapy were used, including "unipolar techniques". Electroencephalograms taken before and after showed no appreciable change even though one of the external electrodes was placed over the scalp covering and just above the undercut portion of the frontal lobe. However, when the same type of current was

directed for the same length of time to the brain through the intracranial electrodes placed subpially above the undercut cortex of the frontal lobe a paroxysmal discharge was demonstrated on the electroencephalogram. It was not accompanied by a clinical convulsion.

**4. EEG in acute head injury. — HARRY A. KAPLAN, ALBERT W. COOK and SAMUEL D. CRITIDES.**

Observations were made on the state of consciousness and the EEG in patients having sustained closed cranio-cerebral injuries, but who have no overlying compressive mass such as a subdural or epidural hematoma. All had had an electroencephalogram within 24 hours following injury. Available evidence indicates that stupor may be related to injury of one or of several regions of the brain and that a dissociation between behavioral and EEG patterns may be obtained. In a study previously reported of stuporous patients harboring subdural hematomas, the EEG, the clinical signs observed on the wards, the pathological findings encountered in the autopsy room, and a consideration of the relevant data obtained from animal experimentation as reported by others, suggested the probable site of pathological disturbance to be in the midbrain. The present study of stuporous patients with brain injury without surface compression suggests the site of major neurophysiological dysfunction to be more rostrally placed, probably in the region of the diencephalon.

**5. Diencephalic influences on performance. — J. R. KNOTT, W. R. INGRAM and R. E. CORRELL, Depts. of Psychiatry and Anatomy, University of Iowa, Iowa.**

Stimulation, via chronic electrodes, in various parts of the diencephalon, has been observed to have distinct effects on learned behavior.

Utilizing cats, trained to press a bar for food reward, "arrest" of the bar-press response can be produced by hypothalamic stimulation, without apparent impairment of other behavior. A "conditioned anxiety" appeared in some animals. Lesions in the hypothalamus may have very profound effects upon learning, and upon retention of a pre-operatively learned act.

**6. Electroencephalographic study comparing effects of neuropharmacological agents on limbic and neocortical structures. — C. KIM and P. D. MACLEAN.**

In an electroencephalographic study comparing the effects of various neuropharmacological agents on limbic and neocortical structures, we have made observations on 20 cats. This paper will be primarily concerned with the results obtained following the administration of reserpine and of ether. About 4 hours after the administration of reserpine, the recording from the hippocampus begins to show a good deal of rhythmic activity at a frequency of 3.5 to 4 c. per sec. This activity is conspicuous only during periods when desynchronized activity of the waking state is recorded from the neocortex. During the next several hours, rhythmic activity becomes much more conspicuous and develops a slower frequency that usually ranges from 2.5-3.5 c. per sec. By the twentieth hour, rhythmic activity may be practically continuous in the hippocampus during long periods when desynchronized activity of the waking state is recorded from the neocortex. Low voltage rhythmic activity that appears to be synchronous with that seen in the hippocampus may also be recorded from the region of the posterior hypothalamus. During the long period when the animal is recovering from the effects of the reserpine, one sees a gradual reversal in the course of electroencephalographic events that have been described. The changes in the heart rate follow a similar time course, there being first a progressive slowing followed by a gradual return to the normal rate. Except for the extended time course, the electroencephalographic picture associated with reserpine has many similarities to that observed during the induction and recovery stages of ether anesthesia. Of the agents we have tested, ether and reserpine are the only ones that have been associated with this distinctive type of electroencephalogram. Brief mention will be made of the findings associated with chlorpromazine, bulbocapnine, and a number of other agents.

**7. Color-shift response in turtle retina and its relation to difference in wave length. — A. FORBES, C. ENROTH, M. NEYLAND, M. S. GONGAWARE and H. W. DEANE. Biological Laboratories, Harvard University, Cambridge, Mass.**

In the turtle all-cone retina color shift evokes an electric response, which cannot be abolished by balancing intensities (*J. Neurophysiol.*, **1955**, *18*: 517). The potential of this response increases as the difference in wave length between the beams is increased. With a deep red interference filter (peak transmission 675 m$\mu$.) for the fixed color and a monochromator for the variable color and with intensities adjusted to equalize the on-effect b-waves evoked by the two beams, the potentials of the shift responses (short to long wave) appear to increase in a stepwise fashion as the wave length of the variable color decreases. The most rapid gains in shift-response potential are found as the variable color passes through the approximate wave-length range 650-630 m$\mu$. (red-orange) and the range 615-695 m$\mu$. (orange-yellow). The reverse shifts (long to short wave) give smaller responses, which appear to show a similar stepwise increase. The stepwise increase suggests that at these wave lengths the color shift produces a maximum increase in the activation of new receptors.

**8. An electroencephalographic study of cerebrovascular hemodynamics in man. — JOHN S. MEYER, HERBERT LEIDERMAN and ROBERT C. STRUZZIERO, Boston, Mass.**

Patients with recurrent cerebrovascular symptoms due to insufficiency of the internal carotid and basilar arteries have been studied electroencephalographically as the blood pressure was lowered by repeated postural tilting (tilt-table) and carotid compression. Such falls in blood pressure may be demonstrated to give rise to transient cerebral ischemia with consequent changes in the EEG. In general, patients with carotid artery insufficiency develop EEG slowing over the Sylvian area and patients with basilar artery insufficiency develop EEG slowing over regions supplied by the posterior cerebral arteries. EEG changes did not appear in a control group including patients with senile and presenile dementia. The combination of cerebrovascular insufficiency and heart disease results in serious liability to postural ischemia of the brain. It has been shown by these studies that insufficiency of the internal carotid or basilar arteries may give rise to episodic syncope, confusion, dementia and seizures. The fall in blood pressure with postural tilting is significantly greater in patients with carotid or basilar artery insufficiency than in a control group without cerebrovascular

disease. Investigation of patients with several types of syncope has shown that a relative insufficiency of the carotid artery may be a contributing factor.

**9. The EEG during anaesthesia with a keto steroid (Viadril). — J. W. Scott and R. A. Gordon, Ont. General Hospital, Toronto.**

Viadril is a 21 hydroxy Keto steroid that has no hormonal effect, but when given intravenously it produces a deep sleep, which, combined with analgesics, provides a good surgical anesthesia. In this series, 5 mg. of Viadril per pound of body weight were administered intravenously in a saline drip over a period of 5 min. At the end of this time the patient would be sleepy, but there was no change in the EEG. In 2 or 3 min. the patient would be deeply asleep, and nitrous oxide and oxygen in the proportions 6:2 was administered as an analgesic. At this time, the EEG shows the maximal change which is reminiscent of the patterns seen in patients receiving full doses of cortisone. The alpha rhythm persists, but it is disturbed by the presence of higher voltage 4-5 c/sec. waves from all head regions, but more prominent from the frontal areas. We did not observe the suppression of the alpha activity that occurs with other forms of anesthesia. Gradually, over the next 15 or 20 min., the slow activity disappears, and a normal waking pattern dominated by the alpha rhythm returns, although the patient is still so deeply asleep that the surgical procedure can be completed with adequate relaxation.

**10. Further observations on sleep state electroencephalograms in brain tumors: Preliminary report. — Daniel Silverman and Robert A. Groff, Graduate School of Medicine, Graduate Hospital University of Pennsylvania, Philadelphia, Pa.**

The delta or theta focus in the waking state EEG's of supratentorial tumors is known to be inconstant during the sleeping state. In sleep the slow wave focus may (1) persist or increase, (2) may be combined with distortion (usually suppression) of sleep spindles or (3) may disappear. Records in these three categories were compared with the operative findings relating to the location, size, depth and type of tumor and the condition of the cortex of the convexity overlying the tumor. In the cases studied thus far, it has been found that (1) records with a persistent delta focus occurred with tumors which were less than 3 cm. from the convexity and over which the convolutions were flattened, widened or discolored; (2) records with a persistent focus and suppression of sleep spindles occurred likewise with tumors which were less than 3 cm. from the convexity but tended to be more superficial, and (3) records with a disappearance of the focus occurred with tumors which were more than 5 cm. from the convexity and over which the cortex was normal. Thus the sleep state EEG when compared with the waking state EEG gave reliable indications of the depth of a tumor.

**11. Effect of medication on interseizure abnormal discharges at different levels of consciousness. — W. F. Caveness and G. Agneu, Neurological Institute, New York, N.Y.**

*Introduction.* During the course of a current investigation of convulsive seizures co-incident with sleep, concomitant observations were made on the effect of medication on abnormal discharges at various levels of consciousness.

*Material and method.* Twenty-one adult patients subject to seizures only, or almost only, during sleep have been individually studied for a period of 20 days and nights. During this time, routine day electroencephalograms were obtained and each night there were continuous recordings during the normal sleeping period, 11 p.m. to 7.30 a.m. During these procedures, each patient received a minimum of 140 hours of recording.

*Drugs.* All medication was gradually withdrawn in each instance. After this there were the following observations: (*a*) Four nights without medication. (*b*) Four nights with Dexedrine sulfate 15 mg. prepared for slow release. (*c*) Four nights with phenobarbital 0.4 g. (*d*) Four nights with Dilantin Sodium 0.4 g.

*Results.* 1. In the 21 patients studied, 5 showed no interseizure abnormal discharges, at anytime, during the waking or sleeping periods. Of these 5, 3 had multiple seizures during the period of observation. 2. Sixteen patients showed abnormal discharges. 3. Of the latter, 8 showed no consistent variation in number of discharges with the administration of the drugs indicated. 4. Eight showed a moderate to marked reduction in abnormal discharges with phenobarbital or Dilantin Sodium.

*Summary and conclusion.* In extensive observation of a small, highly selected group of patients, with seizures coincident with sleep, half of those who had abnormal electrical expressions showed a marked diminution in interseizure abnormal discharges with the administration of phenobarbital or Dilantin Sodium. (*a*) The greatest reduction was in the waking, drowsy or early phase of sleep. (*b*) The least reduction was in the phase of deepest sleep.

This is particularly of interest in that the recordings obtained during induced sleep in routine laboratory examinations seldom affords observations in sleep deeper than the mid level. Thus, many abnormalities may be missed unless medication is withdrawn prior to the electroencephalogram.

**12. Blood ammonia levels, EEG's, and states of consciousness in patients with liver diseases. — J. A. Abbott, Massachusetts General Hospital, Boston, Mass.**

Patients having different kinds of liver diseases which caused disturbances of consciousness were studied for their EEG's, blood ammonia levels, and variations in consciousness from normality to coma. Usually variations in their EEG's from normality to abnormality corresponded with variations in consciousness from normality to coma. A given blood ammonia concentration occurring in different individuals might be attended by very different states of consciousness. Usually in a given individual a sufficient increase in the concentration of blood ammonia was attended by a change of consciousness from better to worse in the range from normality to coma, with corresponding changes in the EEG's. Variations in blood ammonia levels and in consciousness may correspond more closely in those patients who show high, then in those who show low concentrations of blood ammonia. In the group studied the concentrations of blood ammonia nitrogen ranged from 62 to 414 micrograms of ammonia nitrogen per hundred c.c. An individual could show a normal EEG and normal consciousness before or after showing an abnormal EEG and disturbed consciousness. Abnormalities of the EEG's were of two sorts: (1) suppression of

voltages so that well-defined wave-forms were not apparent at least at an amplification of 0.5 cm. for 50 $\mu$V.; (2) a great variety of slow activities which were non-specific except as described by Drs. Foley, Watson, and Adams (*Trans. Amer. Neurol. Ass.*, **1950**, 161-165) and Drs. Bickford and Butt (*J. Clin. Invest.*, **1955**, *6*: 790-799). Examining the same EEG with one among each of the two just-mentioned groups of co-authors showed that the same activity was of the sort described by Drs. Foley, Watson, and Adams as "a blunt spike and a slow wave" and was of the sort described by Drs. Bickford and Butt as triphasic.

**13. Another simple method for the simultaneous cinematographic recording of the patient and his EEG during seizures. — L. F. Stewart, Montreal.**

The camera is positioned vertically over the EEG table and the record photographed normally through a portrait lense placed about 6" in front of the camera lense. A small, surface-silvered mirror is interposed between the camera lense and the portrait lense with its lower edge just above the latter and protruding exactly half way into the camera's field. The surface-silvered mirror faces a second, full length, plain glass mirror positioned over the patient with its long axis parallel to that of the patient, the two mirrors being at the same height above the floor. The large mirror is inclined toward the small at an angle of 45 degrees and the small mirror is inclined away from the large at the same angle.

In this fashion, light entering the left half of the camera lense through the portrait attachment records the image of the EEG on one half of the film. Light entering the right half of the lense from the patient via the two mirrors records the image of the patient on the other half of the film.

This method combines economy and simplicity with good technical results. The method is adaptable to any make or model of camera without the purchase of additional accessories from the manufacturer.

The patient and EEG are seen on the screen in their normal relationships, just as they appear when viewed by an observer in the laboratory.

## ROUND TABLE DISCUSSION ON DEPTH RECORDING

### Eastern Association of Electroencephalographers

**1. The application of depth electrography in some varieties of epilepsy. — Reginald G. Bickford, Section of Physiology, Mayo Clinic and Mayo Foundation, Rochester, Minn.**

In its early phases, the application of depth electrography was in the field of focal epilepsy. With increasing experience, application of the method to more diffuse electroencephalographic disorders has been possible. The latter type of investigation has taken on greater diagnostic significance since the demonstration that some apparently diffuse disorders may arise from a focal brain lesion. To open this symposium on a fairly broad basis, I propose to give a short account of three cases illustrating the application of depth electrography in the diagnosis of three essentially different types of epileptic disorder. The features of the first case are illustrated in the sound movie (movie description).

#### Three illustrative cases

*Case 1.* A man 21 years old complained of attacks characterized by abdominal sensation, dizziness and loss of consciousness with purposeless movements. His seizures were uncontrolled by medication. The electroencephalogram showed a right temporal, sharp-wave focus. Six contact depth leads were implanted in the right temporal lobe and surrounding areas. The movie demonstrates the occurrence of the patient's usual seizures on stimulation of a pair of depth contacts in the region of the right amygdala. The seizure began with a cry, and was associated with a disgusting thought. It was followed by a typical automatism, with swallowing and confusion. Since depth recordings and depth stimulation indicated a deep focal origin for the patient's seizures, probably in the amygdala, Dr. H. J. Svien performed excision of the right temporal lobe, with removal of the amygdala, hippocampus and the overlying cortex. A follow-up report 9 months after the operation showed that the patient had not experienced any more automatisms, and was doing well without taking medication.

*Case 2.* This patient displayed a generalized discharge arising from a focal lesion. The patient was 20 years old and had suffered, since the age of 2½ years, from attacks with sudden loss of consciousness followed by turning of the eyes and head to the right and drawing-up of the right arm and leg. The resting showed bilaterally synchronous spike-and-wave discharge, maximal on the left (secondary bilateral synchrony of Jasper). Multiple depth contacts implanted in both frontal and temporal lobes revealed diffuse spike-and-wave discharge. On stimulation, areas were found on the deep medial surface of both frontal lobes, from which single pulses (5 V., 0.3 msec.) could evoke classical widespread spike-and-wave discharge. This system showed clear recruiting, and was frequency-sensitive at 3 stimulations per sec. (no recruiting at 2 and 4 per sec.). There were, however, no associated symptoms or loss of consciousness and no after-discharge. Stimulation at the rate of 10 per sec. of the left medial frontal cortex produced a typical seizure. On the basis of this evidence, Dr. C. S. MacCarty removed part of the medial cortex of the left frontal lobe. The patient has been free of seizures during the 3 months that have elapsed since operation, and the pattern of the electroencephalogram has returned to normal, without spike-and-wave episodes.

*Case 3.* The condition of this patient, an 11-year-old girl, has been described (*Trans. Amer. Neurol. A.*). Her attacks consisted of typical petit mal, with rolling of the eyes and loss of consciousness. A scalp electroencephalogram showed episodes of classical 3/sec. spike-and-wave discharges associated with attacks of petit mal. In addition, however, there was a right frontal sharp-wave discharge, which on several occasions was noted to initiate the episodes of spike waves. Depth recording was carried out to ascertain the role of focal discharge in the mechanism of seizure. It was found that typical spike-and-wave discharges, with associated attacks of petit mal, could be triggered by single-pulse stimulation over wide areas of

the cortex and subcortex. Since stimulation showed evidence of widespread facilitation, the focal discharge was not considered to be an important part of her seizure mechanism, and surgical treatment was not advised.

### Conclusions

On the basis of these cases the following conclusions may be drawn:

1. Depth recording, and particularly depth stimulation, provide us with a valuable aid in localizing seizure foci situated deeply in inaccessible regions of the subcortex, such as the rhinencephalon and the medial hemispheric areas.

2. A 3/sec. sensitive spike-and-wave system showing recruiting has been isolated.

3. A case has been investigated which shows widespread triggering of spike-and-wave discharge with attacks of petit mal indicative of a diffuse facilitation of cortical and subcortical systems.

*Discussion*:

Andy: What were the parameters of stimulation in the second patient ?

Bickford: 20 c/sec. frequency, 1 msec. pulses monophasic pulses, peak amplitude 10 milli-amps, impedance approximately 200 ohms.

Kellaway: Were the electrode positions varified at operation ?

Bickford: This was not possible. The electrode positions were verified radiologically.

Gloor: Did the 3 c/sec. spike and wave discharges in the second case stop with cessation of stimulation ?

Bickford: Yes. There was no afterdischarge.

Jasper: Was the stimulation always carried out on the left side ?

Bickford: No, but stimulation on the right side did not produce an attack. On the basis of this evidence the excision was carried out. The lesion found at operation was calcified.

Brazier: Did the surface EEG show the same pattern as the depth electrogram during the attack ?

Bickford: On the surface of the frontal lobe the same pattern was seen as in the depth, but the other regions did not participate in the seizure discharge.

Brazier: Was there also recruitment on the surface ?

Bickford: Yes.

Brazier: Is it possible to tell from the record itself if the position of the electrode is on the cortex or in the subcortex ?

Bickford: No.

Grass: Was it a threshold stimulus which produced the seizure discharge ?

Bickford: The stimulus was slightly above threshold intensity.

Sem-Jacobsen: Could this type of seizure discharge only be produced from one contact ?

Bickford: Yes. Other contacts, some on the other side, produced similar but not quite identical responses.

Ajmone-Marsan: How frequent were spontaneous discharges ?

Bickford: They occurred every 10-20 min.

Strauss: What was the spontaneous EEG like ?

Bickford: The spontaneous EEG did not show the same pattern. There was no clear spike and wave discharge.

**2. Depth recording in focal epilepsy. — Peter Kellaway, Baylor University, Houston, Texas.**

The studies reported were carried out in association with Dr. James Greenwood. We have employed depth recording only in patients with epilepsy of focal origin and particularly for the pre-surgical localization and delimitation of foci in cases in which the character of the seizures and/or the EEG findings suggested involvement of deep structures. The technique employed is essentially that developed by Bickford and his associates.

The depth technique has not only been valuable in providing basic information for the planning and carrying out of the surgical removal of epileptogenic foci, but has provided information which has fundamental significance for the understanding of the electrical activity which is recorded from the skull in certain types of cases.

A boy of 5 years had been having uncontrolled focal and generalized seizures since the age of 2½ years. Some of these seizures began with an aura of severe abdominal pain; others with jerking of the left arm. The electroencephalogram revealed what appeared to be a paroxysmal generalized slow spike and wave pattern of a type similar to that called "petit mal variant" by Gibbs and Gibbs. This pattern was, however, asymmetrical with a consistent voltage lateralization to the right side. There were also occasional random slow spike and wave discharges in the right temporal and mid-central electrodes only. Depth electrode studies (carried out over a period of 10 days) revealed independent foci of massive spike discharge in the region of the insula on the right side. At operation, the localization of the electrodes was confirmed and the region of the foci resected. Postoperatively, the electroencephalogram showed some depression over the right temporal region, but no epileptiform activity, either of focal or "generalized" type. This and similar observations confirm the contention we have made elsewhere that in many instances electrographic patterns which are considered to be "diffuse" really arise from deeply lying cortical foci, especially in the temporo-insular regions. The case example given above has been followed for two years post-operatively and there have been no seizures and no evidence of epileptiform activity in the electroencephalogram.

The second case illustrates a problem which is often not recognized — the finding of abnormal focal discharge in the EEG recorded from the convexity which in reality takes its origin not from the region underlying the electrodes, but from buried or mesial cortex at a distance. In this case, a girl of 12 years, the character of some of her seizures suggested an origin in the region of the supplementary motor area and, for this reason, depth electrodes were placed in this region three weeks prior to surgery. Electrocorticography revealed an extensive area in the central region from which almost continuous sharp and slow spike discharge was recorded which would have been difficult to recognize as being of conducted type had the previous depth studies not indicated that this was likely to be so.

The next case illustrates the relationship between what may be recorded at the skull and from the depths in a patient with temporal lobe epilepsy, both in the inter-seizure and seizure periods. Recordings made concommitantly at the scalp and in the depths in

this patient showed consistently that massive repetitive spike and sharp wave discharges may occur in the depth (hippocampus) in the absence of any similar activity in the scalp recording. The presence of abnormal discharges at the scalp did not depend upon the voltage of the discharge taking place in the depth or upon a shift in the locus of the discharging area, but apparently only upon changes in the geometry of the focus and in the character of the discharge. Thus the scalp electrodes may show little change or even a decrease in activity at a time when the seizure activity in the depth may be continuous and of extremely high voltage. At the time that the seizure discharge in the depth becomes sporadic but changes in character, focal sharp or slow waves may appear in the scalp electrodes.

The last case presented is of interest because it shows that patients with epileptogenic foci in the depth may be subject to perceptive, experiential and behavioral disturbances associated with circumscribed seizure discharge activity in the depth at a time when the patient shows no evidence of any other clinical features associated with seizures. For example, this particular patient was, from time to time, quite slow, more mentally dull, had a more flat affect and was quite withdrawn. During the period of study, it was consistently shown that these episodes were associated with almost continuous abnormal activity in the hippocampal region, lasting in some instances as long as three hours. It was also found that this patient had subjective episodes, not associated with overt signs of a seizure, in which she experienced ''thoughts of old things'' and ''distant voices'' crowding in on her mind. These episodes were found to be associated invariably with an increase in the abnormal discharge in the hippocampal electrodes and a fairly consistent change in its character.

*Discussion*:

AJMONE-MARSAN: Was the insula removed in the first patient ?

KELLAWAY: Yes.

AJMONE-MARSAN: Was there any deficit postoperatively ?

KELLAWAY: Yes, there was some weakness but this has almost cleared up by now.

GLOOR: In the third patient, how long after electrode implantation were the records taken which showed the paroxysmal discharges in the hippocampus ?

KELLAWAY: One week after implantation.

WHITE: Was there in this case any evidence for the presence of this hippocampal focus in records taken with naso-pharyngeal or sphenoidal electrodes ?

KELLAWAY: No sphenoidal electrodes were used. The records from nasopharyngeal electrodes did not show any discharges.

**3. Use of intracerebral electrodes in human patients. — José M. R. DELGADO, Yale University, New Haven, Conn.**

In the evaluation of any new technique to be used in human beings, it is important to know the risks of the procedure and to equate them with respect to possible benefit to the patient. The following risks could be predicted in the implantation of intracerebral leads: tissue destruction, hemorrhage, infection, and foreign-body reaction. Our experience with them is based on the study of a group of 30 patients operated upon in collaboration with Drs. Hannibal Hamlin and Yale David Koshoff.

Using 7-lead needle electrodes of only .5 mm. diameter, tissue destruction was probably of no functional significance, and no deficit could be detected in any of our patients. Placement of leads under visual control reduced the danger of piercing a seizable blood vessel and we had no complications in this respect. Sterilization was solved by autoclaving teflon-covered leads and by using high voltage radiation for cortical polyethylene plates. In the patients in whom electrode implantation was the only procedure, no cerebral infections were observed. Two cases of bone button infection were easily curbed with antibiotics. However, after lobotomy (7 patients) and temporal lobectomy (6 cases), performed a few days or a few weeks after electrode implantation, there was one fatality in each group, due in the first to cerebral abcess and in the second to unknown causes.

In our group of mental and intractable pain patients, some with electrocoagulations within the frontal lobes, no epileptic manifestations appeared in any case, in follow-up periods of from one to five years.

With respect to direct benefit to the patient, improvement in the schizophrenics, apart from that which could be explained by greater attention paid to them, was doubtful. Two out of three patients with intractable pain had transitory improvement.

In the group of epileptics, data recorded from depth leads, which could not be obtained by standard electroencephalography, were of great help in diagnoses, and in several cases were of decisive importance in planning or contraindicating surgical operations. In one case, recommended for temporal lobectomy, it was shown that the affected side of the brain was the opposite of that suggested by standard electroencephalography. The use of both cortical, subdural electrodes (plates) and depth leads (needles) seemed to be important in the study of epileptic cases.

Some patterns of electrical activity have been repeatedly observed in different patients and a task for the future may be to study possible causal factors. In our patient a similar distribution of rhythms has been found at corresponding depths of the frontal lobes in different patients, suggesting correlations between anatomical structures and electrical activity. Patients with schizophrenia, intractable pain and anxiety neurosis had a similar distribution of rhythm within the frontal lobes, and no correlation with the type of illness seemed to exist. Opening or closing the eyes had no effect upon surface and depth recording from the frontal lobes. Sound stimulations, such as buzzers or music, increased the amplitude of the electrical activity of motor and premotor areas, but had no influence on the depth recording of the frontal lobes. Voluntary movements, such as turning the pages of a magazine, blocked the fast activity observed in the cortical motor area contralateral to the moving arm. In tape-recorded interviews synchronized with recordings of the electrical activity of the frontal and temporal lobes, it was not possible to establish any correlation between electrical activity and mood or conversation of patients, whether they were silent, talkative, emotionally excited, laughing, or relaxed. Electrical stimulation of the superior temporal convolution, however, was able to induce ''déjà vu'' phenomena, sensory experiences, visual hallucinations, and changes in complex behavior patterns, such as verbalization of feminine striving, in an 11-year old male patient. Electrical stimulation of this area could alter the balance between drive and defense.

In epileptic patients depth recording proved to be very useful from the diagnostic point of view.

Several spontaneous epileptic attacks have been recorded in different patients. In general, chronological and spatial evolution of phenomena were comparable in different attacks in the same patient. In some cases the onset of the electrical disturbance was unilateral, while in some others the onset was bilateral and synchronous in both temporal lobes. We felt that surgery could be useful in the first category, while we advised against surgery in cases where synchronous bilateral involvement was present. Very often, the aura expressed verbally by the patient was also marked in depth recording by the onset of localized abnormal activity. The end of the electrical seizure activity often, but not always, was associated with clinical symptoms, consciousness being recovered in spite of the persistence of gross disturbance of the electrical activity of both temporal lobes.

*Discussion*:

AJMONE-MARSAN: What was the reason to implant electrodes in the patient showing bilateral discharges ?

DELGADO: To establish the localization of the focus of origin of these discharges in a patient showing psycho-motor epilepsy.

JASPER: What was the evidence in this patient that this was a case of temporal lobe epilepsy ?

HAMLIN: This evidence was clinical. The patient suffered from epileptic automatism and there was head turning and chewing during his attack. He also showed assaultive behavior.

JASPER: This might have been a case of petit mal automatism in view of the electrographic pattern which Dr. Delgado demonstrated.

DELGADO: From the electrographic point of view this might well have been so. The diagnosis of temporal lobe epilepsy was based on the clinical symptomatology.

STARK: I wonder if Dr. Jasper would give us his opinion about the criteria by which psycho-motor automatism can be differentiated from petit mal automatism.

JASPER: Petit mal automatism is usually of very short duration. Its EEG criteria are clear and usually unmistakable. However, in a case of petit mal status this differentiation from temporal automatism may be difficult to make on purely clinical grounds, but again the EEG pattern is usually clear enough to settle this diagnostic problem. This is also Dr. Gastaut's opinion.

BICKFORD: In this discussion I detect an implication that perhaps Dr. Delgado's depth procedure is not considered to be justified in the case that he and Dr. Hamlin presented. In my opinion the procedure was well justified since it is in these cases of so called petit mal automatism in which we might well expect to obtain diagnostic information concerning temporal lobe function by the method of depth electrography. It seems to me quite possible that in some of these cases we are dealing with a primary subcortical temporal lobe focus whose firing is triggering the diffuse spike and wave mechanism. Depth recording might provide an excellent opportunity for settling this problem and thereby possibly opening up a surgical approach to the treatment.

HAMLIN: I do not recall specifically the characteristic of the scalp EEG in this patient. But there was no doubt about the diagnosis on the basis of the clinical seizure pattern with automatism and assaultive behavior. The indication for surgical treatment was based upon the findings of depth electrography. One patient who showed focal unilateral disturbances on depth recording with bilateral electrode placements had his temporal lobe on the abnormal side resected with excellent results. Another patient who showed bilaterally synchronous seizure discharges on bilateral depth recording was rejected for operation by Dr. Delgado.

RODIN: I would like to draw your attention towards 2 cases which we have observed in which a classical 3 c/sec. spike and wave discharge lasting for 40-50 sec. was associated with staring, chewing and swallowing movements. The interictal EEG showed a rather marked delta activity over both temporal lobes. I am mentioning these cases in order to inquire whether other members of the group have had similar experiences. The study of such cases may throw some light upon the relationship between certain forms of temporal epilepsy and petit mal.

KELLAWAY: In children 3 c/sec. spike and wave abnormalities are frequently associated with other EEG disturbances, some of which may predominate on one side, most commonly in occipital and frontal regions. A combination between a temporal lobe and a centrencephalic epileptic disorder is certainly possible.

WHITE: We too have been puzzled by cases in which the seizure appeared to be centrencephalic in origin with no cortical focus demonstrated in the EEG and yet clinically these cases showed focal or asymmetrical features. We believe that there may be two possible groups in to which these cases fall. The first group includes patients who probably have pre-existing cerebral damage sometimes due to birth injury or other causes, the presence of which may be suggested by demonstrable neurological signs or more often by asymmetries of the skull, of the subarachnoid sulci or of the ventricular system. The focal cerebral damage underlying these changes perhaps acts on a spreading seizure discharge either by impeding its propagation over the cortex or perhaps by enhancing or focalizing it, thus introducing a focal element into the clinical pattern.

The second group appears only to occur in those convulsions which are prolonged and which, while commencing as symmetrical seizures, later become asymmetrical presumably due to the development of focal cerebral damage from the convulsion. This is suggested by the observation that such seizures are often followed by neurological deficits and dementia which may resolve in a short time or may be permanent. Of course it is probable that in this group too there may have been some-pre-existing focal cerebral abnormality, otherwise the prolonged convulsion would presumably cause diffuse and not localized cerebral damage. Thus these two groups may in fact be the same, different only in the prolongation of the seizure in the second group.

We would like to know what others think about that problem.

PENFIELD: The coexistence of a temporal lobe focus and of centrencephalic discharges has always seemed to me to be of the greatest significance from the point of view of etiology. The temporal focus can be surgically removed leaving only centrencephalic seizures and centrencephalic discharge.

If the anoxia is produced in the mesial zone of the temporal lobe at birth by herniation into the incisura of the tentorium of the adjacent portion of

the temporal lobe, it is conceivable that anoxia may be produced in the brain stem simultaneously. Thus birth compression might produce an anoxic lesion in both areas resulting in the two foci of discharge.

One might suspect that such a situation would sometimes be the original cause of centrencephalic fits in some cases and of temporal lobe seizures in others and occasionally of both types of seizures in the same patient. We certainly need more histological studies of the brain stem of patients who have bilateral 3 c/sec. spike and wave abnormalities.

As to the differentiation of the different types of automatism I may add that as compared with temporal lobe automatism frontal lobe automatism (which results from discharge well forward and usually near the median plane) is apt to be characterized by stereotyped behavior and to be of longer duration. But generalized conclusions are dangerous as the temporal type may be imitated by petit mal automatism and perhaps also by frontal lobe automatism.

BICKFORD: We are impressed on reviewing serial children's records taken over a long period of time that an initial focal discharge may gradually recruit larger areas of the brain and becoming more regular may produce a fairly typical picture of bilaterally synchronous spike and wave discharges. It seems to me that these cases are analogous to the well known monkey experiments in which the normal hemisphere develops a sharp wave abnormality as a result of transcallosal bombardment from an alumina cream focus. In the case of the spike and wave complex we may suppose that firing into the centrencephalic system at first produces a recruited, non sustained response and that in time the system takes on the rhythmic selfsustained and selfinitiated properties of a seizure discharge. This concept of the development of a generalized spike and wave system response from an origin focal discharge obviously has important implications from the depth recording standpoint, since in cases where this mechanism is suspected, a search should be made to locate the primary focus.

KELLAWAY: This sort of time course is often seen in ''jack knife'' — type or ''massive spasm'' — type of seizures which show the electrographic pattern of hypsarhythmia. The early theory to explain this was on the basis of diffuse lesions of the brain. But when these children grow older the EEG becomes more normal or becomes focal again. The generalization of the electrographic abnormality may occur on a purely functional basis.

LIBERSON: I should like to add my observations on unilateral febrile convulsions which I described some time ago under the name of ''convulsive cerebritis''. These children have a unilateral onset of convulsions during a non-specific upper respiratory infection and they may remain unilateral during repeated spells within a period which may last for several hours. There may be a few neurological localizing signs on the same day, but they disappear very promptly. There are no definite findings at lumbar puncture. However in the EEG these children show a unilateral or unilaterally predominating delta activity which subsides very slowly, sometimes within one week or even more slowly. I have observed about 70 of such patients and an observation in these cases, which seems to me to be pertinent to this discussion, of short bursts of 3 c/sec. spike and wave formations. is the frequent occurrence during the follow-up period Some of these children become epileptic, but in none of them did I ever observe any evidence for a true petit mal.

WHITE: Is the delta activity which you observed in these cases not due to the seizures rather than the cause of them ?

LIBERSON: This is a possibility.

I should like to add to Dr. Delgado's observation concerning the persistence of repeated convulsions for a long time after the stimulation of the amygdala in animals, that this may also be observed in man. During a study with Dr. Scoville on psychotic, non-epileptic patients treated by psycho-surgery, we observed that after repeated stimulation of the peri-amygdaloid area several patients had convulsions during the post-operative period. These convulsions subsided many hours after the end of the operation. We did not worry too much about these convulsions, since the very same patients would benefit from a convulsive therapy. None of them developed a chronic convulsive state.

A word of caution should be voiced as to the interpretation of the diagnostic and localizing significance of the origin and the spread of epileptic discharges induced by stimulation. Many of the regions thus stimulated contain structures with a pronounced gradation of the convulsive threshold. In our studies with Dr. Scoville on the uncus in non-epileptic patients we observed that the transmission of the epileptic discharge changes according to the parameters of stimulation and particularly the stimulation intensity. Thus with a liminal stimulation there was a localized discharge or a spread to the contralateral uncus with increasing stimulation intensity there was a progressively increased generalization of the epileptic afterdischarge. We should learn more about these phenomena in non-epileptics before making localizing diagnoses in epileptics.

**4. Correlation of subcortical recordings and behavior. — RUSSELL R. MONROE, Department of Psychiatry and Neurology, Tulane University School of Medicine, New Orleans, Louisiana.**

Two patients with both cortical and subcortically implanted electrodes who showed repeated distinctive correlations between behavior and electrical recordings on the standard Grass 8-channel EEG machine were used as illustrative examples or how with this technique such correlations are possible.

The first patient, a young but chronic and regressed schizophrenic, was followed while receiving a course of twenty-two electric shock treatments. During periods of remission, she showed high amplitude delta activity appearing first in the septal and hippocampal regions but later becoming generalized. By delaying shock treatments, an exacerbation of symptoms would occur while, at the same time, this delta activity disappeared and there was a return to the baseline recording.

The second patient, with a history of episodic psychotic behavior, showed paroxysmal high amplitude theta activity in the septal region and frontal cortex when acutely psychotic. At the same time, there were positive and dyphasic spikes in the hippocampal region not transmitted to the cortex. During periods of remission, this paroxysmal hypersynchronous and spiking activity would disappear. This observation of paroxysmal hypersynchrony in the deep leads but not in the cortex suggests that there might be a close relation between episodic psychotic behavior and psychomotor type epilepsy even when EEG abnormalities are not reported from scalp leads.

*Discussion*:

BICKFORD: What were your criteria for being in the hippocampal region ?

MONROE: The localization of the electrode position was established on the basis of the reading of the stereotaxic instrument and on the basis of the ventriculogram taken with a grid giving a system of coordinates for localizing electrode positions.

AJMONE-MARSAN: Is the rapid activity which you observed in frontal regions affected by movements ?

MONROE: No. This activity is continuous. It is not seen in ordinary scalp EEG's because it is filtered out by the skull and scalp tissue.

**5. Some observations during recording in psychotic patients. — CARL WILHELM SEM-JACOBSEN, Gaustad Mental Hospital, Oslo, Norway.**

In the course of the study first at the Rochester State Hospital, Rochester, Minnesota, and later at Gaustad Mental Hospital, Oslo, Norway, depth recording has been carried out in 105 patients. The electrical activity encountered may be divided into 2 groups:

(1) Activity related to the somatic sensory functions. This activity seems, quite naturally, to be unrelated to mental disorders and seems to be essentially the same whether the patient is or is not suffering from a mental illness.

(2) Activity that seems to be completely unrelated to somatosensory activity.

The presence of arrhythmic 2-4 c/sec. activity in a limited area in the ventromedial part of the frontal lobe has been demonstrated. This activity has been found in all patients studied regardless of clinical diagnosis. Stimulation in this region with a minimal current seems to produce clinical improvement of the patient, and a leucotomy limited to this area also seems to give good ,results.

In a little more than 50 per cent of the patients so far examined high voltage paroxysmal activity of about 2-5 c/sec. also has been found in the ventral part of the frontal lobe. This activity has not been as focal as the arrhythmic 2-4 c/sec. activity. These 2 types of activity have in most cases not been recorded from the scalp. Further study has shown that waves synchronous with the activity just described also appears in areas of the parietal and temporal lobes bilaterally. This activity is not generalized but found only in limited regions. Depth recording during electro- and Metrazol-convulsive treatment has shown further that the changes in the electrical activity of the brain produced by this treatment are most persistent and of longest duration in the ventromedial aspect of the frontal lobe in the area of the arrhytmic 2-4 c/sec. activity. Thus there are several indications that this region is especially important in relation to mental illness.

Examples of depth recordings during spontaneous hallucinatory episodes with agitation in patients with normal preliminary scalp EEG are demonstrated.

There is a sudden marked change of the recording with high voltage activity arising in the parietal region and with synchronous appearance of high voltage activity in the ventromedial aspect of the frontal lobe. Marked changes in the activity in the temporal lobe with high voltage activity appearing in the central part of the lobe is also found. The activity starts and disappears with the hallucination episodes. The patient at this time was arguing with persons known to exist.

*Discussion*:

DELGADO: Paroxysmal activity as described by Dr. Sem-Jacobsen in our experience is not only seen in schizophrenics. We saw the same type of activity in patients with intractable pain.

SEM-JACOBSEN: This has also been our experience.

MONROE: Are there any correlations in your observations between clinical symptoms and the presence of spike-like and sharp wave activity recorded with depth electrodes ?

SEM-JACOBSEN: No, we could not establish such correlations.

AJMONE-MARSAN: If alpha activity is absent on the surface is this also the case in the depth or were you able to record alpha activity in the depth under those conditions ?

SEM-JACOBSEN: Usually when there was no alpha on the surface there was also no alpha in the depth.

MONROE: This is also in accord with our own experience.

KELLAWAY: Temporal lobe activity similar to that observed by Dr. Sem-Jacobsen during hallucinations was also seen in some of our cases in what appeared to be a normal temporal lobe. This activity may only depend on the degree of excitation of the patient and may not be specifically related to hallucinations as such.

SEM-JACOBSEN: It may well be true that this activity is primarily related to a state of nervous tension.

BICKFORD: When patients become agitated they look around a lot and in one slide shown by Dr. Sem-Jacobsen there seemed to be some lambda activity, which might have been related to the visual attention process.

SEM-JACOBSEN: The question of lambda waves must naturally be taken into consideration but the spikes demonstrated in the examples chosen for this presentation do not represent lambda waves. Lambda waves are very easy to detect in recordings from the occipital lobe. In such records fast 27-50 c/sec. waves are consistently found in electrode positions most close to the surface during visual activity. High voltage lambda waves are found in records from contacts about 1 cm. deeper in the cortex. The lambda activity appears to be of extremely focal origin and cannot be seen in recordings from still deeper electrode positions.

It was found that the alpha activity appears with maximum voltage only from a limited area, i.e. from regions deeper than the lambda waves. Thus the spikes and sharp waves seem during the hallucinatory episodes which I have demonstrated in the slide discussed by Dr. Bickford, cannot be lambda waves. It seems clear that we are dealing with a focal spike activity appearing during acute psychotic episodes.

JASPER: It seems obvious to me that besides lambda waves there was certainly some unquestionable abnormality which could not be mistaken for the lambda phenomenon.

BICKFORD: There is, however, some activity which seems to arise from regions very close to the visual system. This is important in view of the fact of the accompanying hallucination.

SEM-JACOBSEN: The electrode position seems to me to be too lateral for visual system.

JASPER: I think that the most important problem to be elucidated in respect with these changes, is whether these changes represent reactions to what happens psychologically to the patient or whether these electrographic changes are primarily related to processes which are the cause of the psychological reactions which were observed.

A question which I would like to ask Dr. Sem-Jacobsen is this: Does he think that the spikes which he recorded during psychotic episodes represent some form of epileptic discharge ?

SEM-JACOBSEN: I believe that this activity is similar to epileptic discharge. I am personally inclined to think that the discharging process is primarily related to the patient's psychotic state.

BRAZIER: Were any spike in the depth synchronous with those on the surface ?

SEM-JACOBSEN: Yes, this was often the case, but the picture was rather confusing. The surface spikes were at times synchronous with discharges arising at one subcortical contact and at another time they would be synchronous with discharges arising from another deep position.

AJMONE-MARSAN: What happens to the paroxysmal activity in the frontal lobe during sleep ?

SEM-JACOBSEN: There is more paroxysmal activity during sleep and the pattern changes often in one typical for physiological sleep discharges. This pattern is rather difficult to differentiate from that seen during wakefulness.

AJMONE-MARSAN: Was this activity seen during wakefulness not perhaps due to some drowsiness ?

SEM-JACOBSEN: No. It was seen in fully awake patients.

KELLAWAY: What happens to this activity with hyperventilation ?

SEM-JACOBSEN: Sometimes it increases, but sometimes it does not change.

STRAUSS: An important question in this respect seems to me to be whether there are any differences in the EEG pattern between schizophrenics with continuous disturbances in their mental state and those showing only episodic disturbances. Were the cases presented by Dr. Monroe and Dr. Sem-Jacobsen a selected group of schizophrenics showing only episodic psychotic manifestations ?

How many of the patients with the clinical diagnosis of schizophrenia did show these paroxysmal EEG changes ? Did their symptomatology or the course of their disease differ from those of schizophrenics without changes in their EEG ?

MONROE: In a selected group of diagnosed schizophrenics who showed episodic psychotic behavior with abrupt onset and abrupt remission lasting a few hours up to a few weeks we found that almost 100 per cent of them showed paroxysmal activity when activated with chloralose. From another study we knew that patients with brain lesions and grand mal epileptics show also activation with chloralose. It is therefore conceivable that this method will give us some clues which could enable us in the future to separate out a specific group of schizophrenics on the basis of electrographic studies.

SEM-JACOBSEN: In a group of psychotics, mostly schizophrenics, paroxysmal high voltage activity is found in depth recording in more than 50 per cent of the patients. A number of these patients have very marked changes in their record during psychotic episodes. These changes resemble the activity most typically seen in epileptics with the presence of a spike focus. These findings indicate that one might have to subdivide the syndrome of schizophrenia on the basis of these findings and they suggest that a great number of schizophrenic patients ought to be grouped in a subcategory closely related to epileptic disorders.

STRAUSS: Lennox and Gibbs once pretended that epilepsy and schizophrenia were basically identical. Later they retraced that statement and restricted it to apply only to cases with episodic psychotic behavior. The opinions which have been expressed by this group tonight seem to confirm this. There may be a group of schizophrenics which one ought to separate from the rest as a circumscribed clinical entity.

JASPER: Better than taking these cases out of the whole group of schizophrenics would be to regard them as cases which may help explain the problem of schizophrenia.

**6. Depth recordings from the amygdaloid region in patients with temporal lobe epilepsy. — MARY A. B. BRAZIER. — Massachusetts General Hospital, Boston, Mass.**

The presentation was specifically restricted to the question of presence or absence of cortical representation (in scalp leads) of abnormal discharges in the depth.

The small series of patients discussed were studied at the Boston Psychopathic Hospital in an investigation under Dr. Harry Solomon directed by Dr. W. P. Chapman to which the present author acted solely as electroencephalographic consultant. The patients all had abnormal EEGs preoperatively, and had clinical seizures of such severity as to cause them to be institutionalized. All had violent automatisms during seizures and all except one had a history of assaultive behavior during such seizures. The shortest duration of seizures was 11 years, the longest 28 years.

The age range was 15 to 43 and in every case it was felt by the psychiatrists that some attempt to salvage these individuals from institutional life should be made. The primary goal of the study was *not* that of depth recording. The goal was to see whether amygdaloid coagulation could be substituted successfully for the major surgery of temporal lobectomy that had been reported by others to be successful in many of these cases. Electrodes were placed stereotactically by measurements derived by Dr. Chapman from a large series of fresh cadavers and by X-ray studies of each patient with air in the temporal horn. The technique of the electrolytic lesions was developed by him through experimentation in animals.

A secondary goal was to use the electrodes implanted for coagulation as recording electrodes in an attempt to assess whether the tissue in which they lay was normal or not, and to determine whether there was any justification for incriminating this region as influential in the production of the individual patient's symptoms by stimulation through these electrodes. The electrodes were left in place for 4-7 days.

Slides were shown illustrating electrical seizure-type discharges in the depth without representation at the cortex. Examples were also shown of the final

stages of electrical seizure patterns with the familiar development of periods of electrical silence interrupting the spiking at increasingly frequent intervals. A common finding is that after such periods of silence the first spike only of each intermittent burst is represented at the cortex. Slides were also shown of singly occurring spikes in the depth and some evidence was presented to show that with the three-dimensional (but not truly Laplacian) electrode array used, i.e. with 4 recording points in the depth, some field diagrams could be prepared that fulfilled the amplitude and phase characteristics of the empirical findings. Some evidence was presented that, in any one individual, the field of the spike at the depth had some relation to its having representation or not in the scalp leads over the temporal convexity.

A suggestion was outlined for a more efficient method of investigating the relationship between depth and surface recordings by application of the cross-correlation techniques that have been developed in collaboration with the Research Laboratory of Electronics at Massachusetts Institute of Technology. These were described in brief and some slides of sample cross-correlations were shown.

*Final discussion*:

BRAZIER: Dr. Jasper has asked me to attempt a summing up of the papers we have heard today. Here are some of the thoughts that ran through my mind as I listened to the speakers and to the questions from the floor.

There seem to have been several different goals in the minds of the various workers who have implanted depth electrodes in man and these may be broadly classified in 3 categories:

(1) *Recording*: to learn the characteristics of the electrical activity in sub-cortical structures in both physiological and pathological conditions, and to gain information for diagnosis in the latter.

(2) *Stimulation*: as an activation procedure for diagnosis, and (in Dr. Monroe's series only) as a possible therapeutic procedure.

(3) *Coagulation*: as a possible substitute for major surgery (in the case of the Boston Psychopathic Hospital's series).

The third of these categories has not been discussed here so I shall not refer to it again. In fact most of the reports have been concerned with the first category: that of recording. In his opening remarks, Dr. Jasper expressed the hope that this Round Table might contribute to an assessment of depth recording that would enable us to decide whether this line of work was worth developing farther. It is clear from these reports that this work is still wholely empirical and still in the descriptive stage that most branches of science go through in their early days. The next step is the difficult one and one wonders how it can best be approached. Here are a few suggestions:

(1) A clearer understanding of volume conductor theory is required and a more intensive study of what Dr. Kellaway has called "the electrical geometry" within the brain is necessary before these empirical results can have real meaning. These are extracellular potentials that we record with electrodes of this size. Fields of extracellular current flow lying among densely packed parallel fibers differ greatly in shape (and hence in current density) from the more open fields of sparsely populated cell aggregates, for example. Another problem for study is the relatively restricted field of a spike potential compared with the widespread field of a slow wave.

Other points in volume conductor theory were reflected in some of the slides shown today. Of the spikes illustrated, some were triphasic in form suggesting that they may have been the sign of events travelling past the recording electrode. Others were monophasic and negative in sign suggesting that they may have arisen at the site of the recording point. The speakers did not make this distribution. Also implicitly, if not explicitly, recordings were presented as activity arising in the brain structures in which the electrodes lay, whereas the available evidence is only that, of the limited number of electrodes implanted, a given one was nearer to such activity than were the others. This is almost a problem in the framework of Bishop Berkeley's philosophy. Who knows what the activity is where no electrodes are lying ?

In addition to the electroencephalographer's need to understand his recordings in terms of electrophysiology are the clinical questions as to the significance of electrical seizure-type discharges in the depth without clinical signs, and the familiar and vexing problems as to the rationale for either coagulation or surgical removal of electrical foci when stimulation of such regions does not mimic the patient's spontaneous seizures. Does stimulation necessarily give information about neuronal connections or even of neuronal influences ? We have seen examples today from Dr. Bickford of triggering of the wave-and-spike in a very wide area and Dr. Liberson has brought up the related problem of the transmission of after-discharges. I would like to hear these points discussed by the other members of the Round Table.

JASPER: It is unfortunate that time does not permit the continuation of this discussion much longer. I am afraid we will not be able to consider many of the important questions raised by Dr. Brazier, but they have given us much to think about.

With regard to the future work in depth recording it seems to me that this Round Table discussion has emphasized at least three major requirements before much of this data can be adequately interpreted and more significant results obtained (1) It is necessary to have better methods for the exact localization of the position of the implanted electrodes. (2) The variations in electrical activity which may be obtained from depth electrodes in normal brain will have to be determined before we can interpret many of the observations we are now obtaining from patients with various brain disorders. (3) Finally we are sorely in need of working hypotheses so that the placement of electrodes in cortical and subcortical structures will be made more systematically for a definite purpose, and stimulation and recording carried out to test specific hypotheses rather than in a random exploratory manner.

# *BOOK REVIEWS*

Edited by CHARLES HENRY

## DIENCEPHALON. AUTONOMIC AND EXTRAPYRAMIDAL FUNCTIONS

WALTER RUDOLPH HESS

Grune and Stratton, New York. 1954, 79 pp., $4.00

The work of Professor Hess, which has been rewarded by a Nobel Prize, has perhaps not received all the attention it deserves, especially in English-speaking regions. This is not because scientists in these areas were unaware of the Hess technique and its results, nor because of inaccessibility of the recorded data, but rather because of a certain opacity of style in the original German. This attractive little book is therefore welcomed by persons interested in the field, not so much for description of methods and results, but for its expression of the author's scientific philosophy.

Summarizing a series of lectures given at Harvard, Hess briefly describes the method of implanting stimulating electrodes which he has used for many years in a total of 480 experiments, cinematographically recorded in unanesthetized animals. This is not a stereotactically controlled method, but nevertheless is a delicate one which also makes possible the production of lesions at the sites previously explored with stimulation. More recently in other laboratories stereotaxic methods have been combined with electrode implantation in ways which have perhaps added lability to this approach. The reader interested in Hess' method will need to refer to his monograph of 1932 (Die Methodik der localisierten Reizung und Ausschaltung. G. Thieme, Leipzig). In the brief summary given in the current work the author's ideas on electrical stimulation are presented, including a denial that the low voltage, low frequency parameters used produce tissue damage, which is somewhat surprising since frequencies of 2 to 8 per sec. were used. Other workers have observed tissue destruction even with frequencies of 80 to 300 per sec., provided there was a sufficient total elapsed time of stimulation. Histological evaluation of the stimulus sites was carried out after production of lesions. This enormous material has not as yet been completely studied by degeneration techniques, but is still under scrutiny by some of Hess' followers.

The description of Hess' results is brief but lucid and will be welcomed by scientists not directly concerned with the field. It offers no substitute for the original papers, however, and even the summary by Gloor (*Arch. Neurol. Psychiat.*, **1954**, *71*: 773) is more adequate. A number of points must be stressed including the following: (1) various functions are grouped within extended areas, (2) these areas overlap, (3) individual signs or functions are not coordinated with individual nuclei. Many workers can concur with these views up to a point. However, nuclear designation is valuable at least for purposes of description and Hess' published works might have gained clarity if morphology had received more attention.

Hess associates the anterior part of the hypothalamus, the preoptic and septal areas with protective mechanisms in a so-called trophotropic or endophylactic zone, which acts mainly through the parasympathetic system. In more posterior regions of the diencephalon is a dynamogenic or ergotropic zone, concerned with bodily work. Stimulation of the latter evokes collective results, while stimulation of the former may produce individual effects. This view is not supported by all students or followers of Hess. Other areas of the diencephalon are associated with sleep, atony and adynamia. Production of sleep by stimulation is not unanimously agreed upon, for some workers have not been able to reproduce the Hess results, although a tranquilizing effect of prolonged stimulation has been noted. The production of aggressive, affective patterns of behavior was also described, which, surprisingly, Hess gives some subjective value and proposes that the hypothalamus can influence cortical reactions and inhibitions.

Statokinetic effects of diencephalic stimulation were observed and given dynamic appellation with the terms teleokinetic (for voluntary directed motion) and ereismatic (for basic support of motion). These coordinated responses have been observed by others and related to posture and movement. Hess' statement that "every expression of the dynamics of the skeletal muscles is the manifestation of the regulating activity of the corresponding center", which is a well-stated aphorism, will come as no surprise to any student who has completed a well organized course in neuroanatomy. In spite of the drawbacks of this portion of the book, Hess renders a signal service by his representation of the term *center* and should be quoted.

"Physiologically the center is a device to establish connections, which is dependent upon the peripheral situation, and whose organization is directed toward a definite result. Nervous elements located at very different levels of the nervous system may constitute a center. It is not wrong to consider as a part of the coordinating apparatus, that is, of the functional center, even the primary representatives of the sensory receptors, as well as those of the motor effectors. In any event, to attribute the central function of organization to a circumscribed structure, even to a conglomeration of cells or a nucleus, is a concept which must be rejected. A center is represented by a series of polysynaptic connections from among which — under the controlling influence of the peripheral situation — those connections are selected which give the appropriate pattern of a directed motion."

Included in the book is a short chapter on autonomic effects and the frontal lobe in which combined somatic and autonomic activities are discussed. From Hess' viewpoint, cortical influence on autonomic activity is indirect. For instance, there is no direct connection involved when blood pressure rises during anger, or when defecation occurs due to fear. He does not believe there is evidence for true autonomic cortical function, but that the cortex belongs to the "instrumentarium of exteroverted functions".

Prospects for future research are considered, also briefly. Among the proposed lines are: (1) continued attack on problems concerned with influences of the central gray upon the cortex, including anatomic demonstration of connections subserving sleep and emotion; (2) study of the coordinating function of the substantia reticularis; (3) definition of the structure of a so-called center; (4) study of the topography of consciousness, although the author has doubts concerning the proper statement of this problem; (5) extension of the stimulation method to more extended areas in order to define more clearly the fiber systems and cell groups concerned in the responses. Hess also speaks with optimism regarding collaboration between biochemistry and physiology, especially in the study of humoral agents, and he also stresses the necessity for comprehensive planning for research which would include morphology and comparative physiology.

The final section of the book, entitled Integration of Autonomic Functions is a rather general, almost elementary discussion of interlocking autonomic activities, including local spontaneous or induced activity, regional activity and the coordination of such activities for the general organismic good by central nervous mechanisms. Surprisingly he suggests that some reflex arcs are completed in prevertebral ganglia, in spite of a considerable body of evidence to the contrary. However, the importance of "super-segmental" coordinating systems is stressed again here, as it was in the earlier chapters. The advantage of thinking in terms of a coordinated process is pointed out in view of the opportunity it offers for understanding the interplay between sympathetic and parasympathetic systems. He even intimates that the morphologic terms sympathetic and parasympathetic should be abandoned in favor of functional terms such as *ergotropic*, or energy system, and endophylactic-trophotropic system for protection and restitution. Hess returns again here to his previously mentioned concept of a "center" and reemphasizes the importance of the diencephalon for autonomic regulation, offering the opinion that "it can hardly be wrong to regard the diencephalon, rather than the cortex, as the true central organ of the body".

Review of this book may well be concluded by citing its final provocative paragraph.

"Finally, we come to the question of whether the autonomic regulation exerted by the diencephalon is not ultimately dependent on cortical control. This was discussed extensively in Part I. There, the reasons were given which led to the conviction that the production of autonomic effects by stimulation of certain areas of the cortex requires a different interpretation. Where it is not merely a question of irradiation we must take account of the fact that all psychic processes which are accompanied by affective manifestations cause a displacement in the equilibrium of the autonomic nervous system. Therefore, I conclude this treatise with a repetition of my conviction that true autonomic regulation finds its highest level of direct and automatic coordination in the diencephalon."

A valuable bibliography of the published works of the Hess school is included in the book. References to the work of others is, however, very limited.

W. R. INGRAM

# LABORATORY INSTRUMENTATION IN PSYCHOLOGY

WILLIAM W. GRINGS

The National Press, Palo Alto, California, 1954, 282 pp.
$4.75 (cloth), $4.00 (paper)

This book is a survey of instrumentation used in psychological experiments. It is intended primarily for the graduate student and for those professional people who desire a background in techniques of recording and controlling behavioral phenomena. There is a section on bioelectricity that offers nothing new to the average electroencephalographer. Rather, the value of this book for the EEGer lies in the material presented from other fields. There is a general section on behavior recording apparatus and another on timing and counting techniques. These are followed by chapters dealing with special instrumentation for research in vision, audition and other senses. An additional section is devoted to apparatus used in studies on memory, learning, problem solving and perception.

An attempt is made to present some of the basic principles underlying recording and measurement systems, introducing a certain amount of elementary physics as background material. However, this is rather poorly integrated with the descriptions of the instruments themselves, so that there is a frequent discontinuity in the text. Granting that it would be difficult to cover the theoretical aspects of apparatus described, one is left with a feeling of incompleteness in some areas. The author corrects for this in part by giving rather extensive bibliographic material.

Perhaps the most valuable feature of the book is that it introduces the reader to a variety of methods for controlling, as well as recording, experimental variables. Practical considerations are given to the selection of equipment to fit a given experiment, with the limitations of instruments clearly emphasized. For example, in presenting galvanic skin response, there is first a brief description of the two types of electrodermal phenomena. This is followed by a discussion of electrodes and how to handle problems of electrode polarization. Several types of circuit are then described, with emphasis on sensitivity, recording range, constant current through the subject, etc. Instrument response characteristics, distortion problems and artifacts are also treated at appropriate points throughout the text. Many photographs and diagrams, not always particularly relevant or well labelled, are liberally presented.

Although the book deals inadequately with the "why" of instrumentation (a purpose for which it was not written), it does a good job at surveying the "how", by pointing the way to numerous applications that the uninitiated experimenter can draw on. For this reason it can be of definite value to EEGers embarking on work with psychological variables.

WALTER D. OBRIST

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